171 (1) No. 10- Supreme Court, U.S. FILED

IN THE
Supreme Court of the United States

10-426 SEP 23 2010

OFFICE OF THE CLERK

APPLERA CORP. AND TROPIX, INC.,
Petitioners,

v.

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., AND YALE UNIVERSITY,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

NICHOLAS GROOMBRIDGE
JENNIFER H. WU
WEIL, GOTSHAL & MANGES LLP
767 Fifth Avenue
New York, NY 10153
(212) 310-8000

ANTON J. BOKAL
ALAN W. HAMMOND
KURTIS D. MACFERRIN
LIFE TECHNOLOGIES CORP.
850 Lincoln Centre Dr.
Foster City, CA 94404
(650) 554-3410

CARTER G. PHILLIPS*
ERIC A. SHUMSKY
RACHEL TOWNSEND
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, DC 20005
(202) 736-8000
cphillips@sidley.com

TACY F. FLINT
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, IL 60603
(312) 853-7000

JOHN M. WHEALAN
12 Sunnyside Road
Silver Spring, MD 20910
(202) 994-2195

Counsel for Petitioners

September 23, 2010 *Counsel of Record

WILSON EPES PRINTING CO., INC. (202) 789-0096 - WASHINGTON, D.C. 20002

QUESTION PRESENTED

For a patent to be valid, its claims must be "definite"—the patent must include "claims *particularly pointing out* and *distinctly claiming* the subject matter which the applicant regards as his invention." 35 U.S.C. § 112 ¶ 2 (emphasis added). The Federal Circuit holds that this requirement of "particular[ity]" and "distinct[ness]" is satisfied so long as claim language is not "insolubly ambiguous," or is merely capable of being construed. The question presented is:

Whether the Federal Circuit's standard for definiteness is consistent with the language of § 112.

PARTIES TO THE PROCEEDING

All parties to the proceeding are identified in the caption.

RULE 29.6 STATEMENT

Petitioner Applera Corporation was formerly made up of two business units, Applied Biosystems and Celera Genomics. In 2008 Applied Biosystems merged with a subsidiary of Invitrogen Corporation to form Applied Biosystems, LLC. Celera Genomics has been split off into an independent company, Celera Corporation.

Invitrogen Corporation is now known as Life Technologies Corporation, and wholly owns Applied Biosystems, LLC. Celera Corporation and Life Technologies Corporation are both publicly traded. No publicly held company owns more than 10% of either Celera Corporation's or Life Technologies Corporation's stock.

Tropix, Incorporated was purchased by Applera Corporation and no longer exists as a separate legal entity.

TABLE OF CONTENTS

	Page
QUESTION PRESENTED	i
PARTIES TO THE PROCEEDING	ii
RULE 29.6 STATEMENT	ii
TABLE OF AUTHORITIES	v
OPINIONS BELOW	1
JURISDICTION	1
STATUTORY PROVISION INVOLVED	1
INTRODUCTION	2
STATEMENT OF THE CASE	4
I. STATUTORY BACKGROUND	4
II. THE TECHNOLOGY AT ISSUE	7
III. PROCEEDINGS BELOW	10
REASONS FOR GRANTING THE PETITION	15
I. THE FEDERAL CIRCUIT HAS DEPARTED FROM THE TEXT OF § 112 AND THIS COURT'S PRECEDENTS CONSTRUING IT.	16
A. The Statutory Language Requires That Patent Claims Be Defined With Particularity And Distinctness.	16
B. The Federal Circuit Requires Only That Patent Claims Not Lack Total Ambiguity.	18
II. THE FEDERAL CIRCUIT'S INTERPRETATION OF § 112 CONFLICTS WITH THE PTO'S	23

TABLE OF CONTENTS—continued

Page

III. THE DECISION BELOW IS A GOOD VEHICLE FOR RESOLVING THESE ISSUES 26

CONCLUSION 30

APPENDIX A: *Enzo Biochem, Inc.* v. *Applera Corp.*, 599 F.3d 1325 (Fed. Cir. 2010) 1a

APPENDIX B: *Enzo Biochem, Inc.* v. *Applera Corp.*, No. 3:04cv929 (JBA), 2007 WL 2669025 (D. Conn. Sept. 6, 2007) 34a

APPENDIX C: *Enzo Biochem, Inc.* v. *Applera Corp.*, 605 F.3d 1347 (Fed. Cir. 2010) 74a

APPENDIX D: Expert Report of Larry J. Kricka, D.Phil., *Enzo Biochem, Inc.* v. *Applera Corp.*, No. 3-04-CV-929 (JBA) (D. Conn. filed Aug. 18, 2005) 80a

TABLE OF AUTHORITIES

CASES Page

ALZA Corp. v. *Andrx Pharms., LLC*, 603 F.3d 935 (Fed. Cir. 2010) 6, 24
Ariad Pharms., Inc. v. *Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) 24
Bd. of Regents v. *BENQ Am. Corp.*, 533 F.3d 1362 (Fed. Cir. 2008) 20
Bilski v. *Kappos*, 130 S. Ct. 3218 (2010) 3
Bonito Boats, Inc. v. *Thunder Craft Boats, Inc.*, 489 U.S. 141 (1989) 4, 24
Datamize LLC v. *Plumtree Software, Inc.*, 417 F.3d 1342 (Fed. Cir. 2005) 20
Exxon Research & Eng'g Co. v. *United States*, 265 F.3d 1371 (Fed. Cir. 2001) 18, 21
Festo Corp. v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002) 17
Fuji Photo Film Co. v. *ITC*, 386 F.3d 1095 (Fed. Cir. 2004) 5, 22
General Electric Co. v. *Wabash Appliance Corp.*, 304 U.S. 364 (1938) 16, 17, 21, 27
Hearing Components, Inc. v. *Shure Inc.*, 600 F.3d 1357 (Fed. Cir. 2010) 21
Holland Furniture Co. v. *Perkins Glue Co.*, 277 U.S. 245 (1928) 27
Honeywell Int'l, Inc. v. *ITC*, 341 F.3d 1332 (Fed. Cir. 2003) 18
Honeywell Int'l Inc. v. *United States*, 609 F.3d 1292 (Fed. Cir. 2010) 19
The Incandescent Lamp Patent, 159 U.S. 465 (1895) 16
Jimenez v. *Quarterman*, 129 S. Ct. 681 (2009) 24
Keystone Bridge Co. v. *Phoenix Iron Co.*, 95 U.S. 274 (1877) 24

TABLE OF AUTHORITIES—continued

Page

Kinetic Concepts, Inc. v. *Blue Sky Med. Group, Inc.*, 554 F.3d 1010 (Fed. Cir.), *cert. denied*, 130 S. Ct. 624 (2009) 21

KSR Int'l Co. v. *Teleflex, Inc.*, 550 U.S. 398 (2007) 3, 6

Ex parte Kubin, 83 U.S.P.Q.2d 1410 (B.P.A.I. 2007), *aff'd*, 561 F.3d 1351 (Fed. Cir. 2009) 24

Markman v. *Westview Instrs., Inc.*, 517 U.S. 370 (1996) 3, 4, 5

Merrill v. *Yeomans*, 94 U.S. 568 (1876) 16, 17

Ex parte Miyazaki, No. 2007-3300, 2008 WL 5105055 (B.P.A.I. Nov. 19, 2008) 4, 23, 24

In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988) 7

Permutit Co. v. *Graver Corp.*, 284 U.S. 52 (1931) 6, 17, 28

Phillips v. *AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) 5

Power-One, Inc. v. *Artesyn Techs., Inc.*, 599 F.3d 1343 (Fed. Cir. 2010) 19

Source Search Techs. LLC v. *LendingTree LLC*, 588 F.3d 1063 (Fed. Cir. 2009) 18

Ultimax Cement Mfg. Corp. v. *CTS Cement Mfg. Corp.*, 587 F.3d 1339 (Fed. Cir. 2009) 18, 19, 20

United Carbon Co. v. *Binney & Smith Co.*, 317 U.S. 228 (1942) ..... *passim*

Universal Oil Prods. Co. v. *Globe Oil & Ref. Co.*, 322 U.S. 471 (1944) 4

White v. *Dunbar*, 119 U.S. 47 (1886) 16

Young v. *Lumenis, Inc.*, 492 F.3d 1336 (Fed. Cir. 2007) 18, 20

TABLE OF AUTHORITIES—continued

CONSTITUTION AND STATUTES

	Page
U.S. Const. art. I, § 8, cl. 8	4
28 U.S.C. § 1295(a)	4
35 U.S.C. § 2	4
35 U.S.C. § 102	6
35 U.S.C. § 103	6
35 U.S.C. § 112	2, 5, 6, 16

OTHER AUTHORITIES

U.S. Dep't of Commerce, *Manual of Patent Examining Procedure* (8th ed. Rev. 2010)	10
U.S. Patent No. 5,328,824	9, 10
U.S. Patent No. 5,449,767	9, 10
U.S. Patent No. 5,476,928	9, 10

PETITION FOR A WRIT OF CERTIORARI

Applera Corporation and Tropix, Incorporated (collectively, "Applera") respectfully petition for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The opinion of the United States District Court for the District of Connecticut, which granted summary judgment to Applera that the patent claims asserted by Respondents are invalid, is available at 2007 WL 2669025, and is reproduced in the appendix to this petition (Pet. App.) at 34a-73a. The opinion of the Federal Circuit is reported at 599 F.3d 1325, and reproduced at Pet. App. 1a-33a. The Federal Circuit's order denying panel rehearing and rehearing en banc, accompanied by Judge Plager's opinion dissenting from the denial of panel rehearing, is reported at 605 F.3d 1347, and reproduced at Pet. App. 74a-79a.

JURISDICTION

The court of appeals entered judgment on March 26, 2010. Pet. App. 1a. A timely petition for rehearing and rehearing en banc was denied on May 26, 2010. Pet. App. 74a-75a. The jurisdiction of the court of appeals was based on 28 U.S.C. § 1295(a)(1). On August 11, 2010, Chief Justice Roberts granted an extension of time to and including September 23, 2010, to file a petition for a writ of certiorari. This Court has jurisdiction pursuant to 28 U.S.C. § 1254(1).

STATUTORY PROVISION INVOLVED

The federal Patent Act provides in relevant part as follows:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. § 112 ¶ 2.

INTRODUCTION

The statutory requirement of definiteness—that a patent's claims "*particularly* point[] out and *distinctly* claim[] the subject matter which the applicant regards as his invention," 35 U.S.C. § 112 ¶ 2[1]—is of surpassing importance. It is a basic requirement that must be satisfied for a patent to be issued or enforced, and so it affects every pending U.S. patent application, every issued U.S. patent, and many if not all U.S. federal-court patent cases. This requirement also is central to the proper functioning of the patent system. At the heart of that system is a basic bargain: Inventors are granted a limited monopoly in exchange for making their invention public. For this system to operate fairly and effectively, the inventor must provide clear notice to the public of the invention's metes and bounds, or else the patent system will discourage rather than encourage invention:

> "[T]he limits of a patent must be known for the protection of the patentee, the encouragement of the inventive genius of others and the assurance that the subject of the patent will be dedicated ultimately to the public." Otherwise, a "zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field,"

---

[1] Emphases are added throughout this petition unless otherwise noted.

> and "[t]he public [would] be deprived of rights supposed to belong to it, without being clearly told what it is that limits these rights."

Markman v. *Westview Instrs., Inc.*, 517 U.S. 370, 390 (1996) (alterations in original) (quoting *General Electric Co.* v. *Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938); *United Carbon Co.* v. *Binney & Smith Co.*, 317 U.S. 228, 236 (1942); and *Merrill* v. *Yeomans*, 94 U.S. 568, 573, (1877)).

Since this Court last addressed the fundamental requirement of definiteness more than half a century ago, the Federal Circuit has departed radically from the statute's language, in derogation of the patent system's basic purpose. In this and a series of other cases, that court has created precisely the "zone of uncertainty" that this Court declared antithetical to innovation. In the decision below, the Federal Circuit concluded that a patent is definite where it provides "at least some guidance" about the boundaries of its claims. Pet. App. 14a. This toothless standard is emblematic of the Federal Circuit's basic approach, articulated in this case and elsewhere, that a claim is definite if it is merely "capable of being construed" or, put otherwise, not "insolubly ambiguous." In short, here as elsewhere, the Federal Circuit has adopted a rule that departs from the statutory language and does serious violence to the statutory purpose. Cf. *KSR Int'l Co.* v. *Teleflex, Inc.*, 550 U.S. 398, 415-18 (2007) (rejecting the Federal Circuit's "TSM" test for obviousness); *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3225-26 (2010) (rejecting "machine-or-transformation" test as the sole test for determining the patentability of business methods).

This Court's review also is warranted because the Federal Circuit's test for indefiniteness conflicts with the more rigorous standard adopted by the Patent

and Trademark Office (PTO). The PTO has flatly rejected the Federal Circuit's "insolubly ambiguous" standard, and employs a more demanding standard for definiteness—i.e., it uses "a lower threshold of ambiguity when reviewing a pending claim for indefiniteness than those used by [the Federal Circuit]." *Ex parte Miyazaki*, No. 2007-3300, 2008 WL 5105055, at *5 (B.P.A.I. Nov. 19, 2008). This conflict is unsustainable. "One of the fundamental purposes behind the Patent and Copyright Clauses of the Constitution was to promote national uniformity in the realm of intellectual property." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 162 (1989); accord *Markman*, 517 U.S. at 390 (noting "the importance of uniformity in the treatment of a given patent"). This Court should grant certiorari to resolve this conflict between the federal agency that has responsibility for granting and issuing patents, see 35 U.S.C. § 2, and the federal appeals court that has exclusive appellate jurisdiction over patent litigation, see 28 U.S.C. § 1295(a). In the alternative and at a minimum, this Court should call for the views of the Solicitor General, as it has done in other recent cases presenting important questions arising under the Patent Act.

STATEMENT OF THE CASE

I. STATUTORY BACKGROUND

"The Congress shall have power ... [t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art. I, § 8, cl. 8. Congress has effectuated this constitutional imperative by granting to inventors limited exclusivity in exchange for "precision of disclosure" of what they have invented. *Universal Oil Prods. Co.* v. *Globe Oil & Ref. Co.*, 322 U.S. 471, 484

(1944) ("[T]he *quid pro quo* [for the patent right] is disclosure of a process or device in sufficient detail to enable one skilled in the art to practice the invention once the period of the monopoly has expired, and the same precision of disclosure is likewise essential to warn the industry concerned of the precise scope of the monopoly asserted.").

In establishing the patent system, Congress enacted statutory requirements dictating how patents must be structured and limiting what they may cover. 35 U.S.C. § 112 requires each patent to include a "specification." The specification must "contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use" the invention. 35 U.S.C. § 112 ¶ 1. Section 112 further requires that the specification "conclude with one or more claims *particularly pointing out* and *distinctly claiming* the subject matter which the applicant regards as his invention." *Id.* ¶ 2. If a patent is granted, it is these "claims" (rather than the specification, for instance) that set the boundaries of the patent right. *Markman*, 517 U.S. at 373; see also *Fuji Photo Film Co.* v. *ITC*, 386 F.3d 1095, 1106 (Fed. Cir. 2004) ("[i]t is a familiar axiom of patent law" that limitations in the specification are not to be imported into the claims).[2]

A single patent may contain multiple claims, and indeed this is common practice. Each claim may form

---

[2] The first step in patent litigation is typically "claim construction," the process of interpreting the language used in the claims. *See, e.g.*, *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1312-19 (Fed. Cir. 2005) (en banc). In construing claim language, the reviewing court attempts to determine how a person of ordinary skill in the art would understand the terms. *Id.* at 1313.

the basis for a claim of infringement. Here, for instance, one of the three patents at issue contained 71 separate claims. Federal Circuit Joint Appendix ("CAFC JA") 182-85. Some of those claims were "independent"—i.e., they were freestanding and did not refer to any other claims in the patent. Others were "dependent"—they incorporated the limitations set forth in a previous claim in the patent, and added some further limitation. See 35 U.S.C. § 112 ¶¶ 3-4.

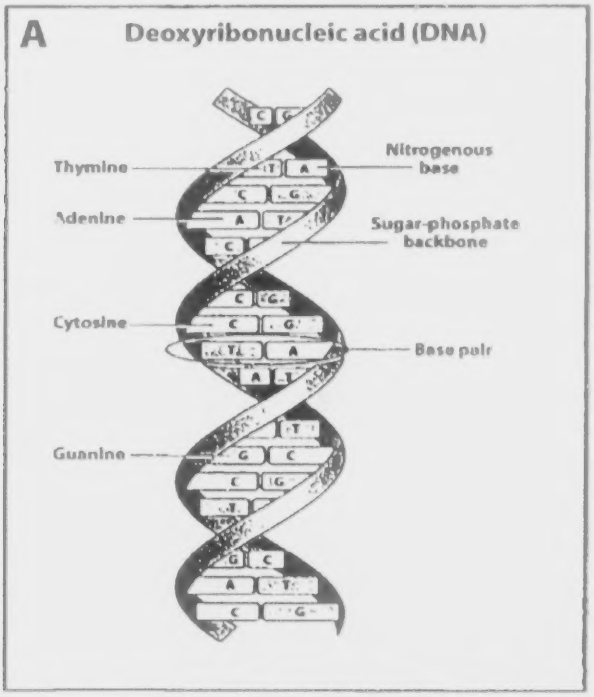
Separate from whether a patent has been infringed-- a question that is not at issue in this appeal—is whether a patent claim is "valid." The Patent Act establishes various bases upon which a claim may be invalid, and these operate as defenses to a claim of infringement. If, for instance, a claim is so broad that it covers what already has been done or disclosed, it is invalid for lack of novelty. See *id.* § 102. If a claim merely covers obvious modifications to what previously has been done or disclosed, then a patent is invalid for "obviousness." *Id.* § 103; see *KSR*, 550 U.S. at 417-18. If the patent specification does not provide a description that would permit one of ordinary skill in the art to implement the full scope of what is claimed without undue experimentation, the claim is invalid for lack of enablement. See, *e.g.*, *ALZA Corp.* v. *Andrx Pharms., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010).

And, pertinent here, if the claim does not "particularly point[] out and distinctly claim[]" the invention, then it is invalid as "indefinite." 35 U.S.C. § 112 ¶ 2. Definiteness serves a critical notice function: A claim must "inform the public during the life of the patent of the limits of the monopoly asserted, so that it may be known which features may be safely used or manufactured without a license and which may not." *Permutit Co.* v. *Graver Corp.*, 284 U.S. 52, 60 (1931).

This "statutory requirement of particularity and distinctness in claims is met only when they clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." *United Carbon*, 317 U.S. at 236.

II. THE TECHNOLOGY AT ISSUE

This litigation involves a dispute over patents concerning technology for detecting nucleic acids such as DNA and RNA. See Pet. App. 2a, 4a-5a. DNA and RNA store in coded form the genetic information in human cells. See generally *In re O'Farrell*, 853 F.2d 894, 896-98 (Fed. Cir. 1988). They are composed of nucleotides that are linked together to form "polynucleotide" chains. This diagram shows two such chains joined together in the famous "double helix":



CAFC JA 7527.[3]

Important to the structure of the nucleotides—and to the diagnostic technology at issue here—are nitrogenous bases. These bases form the rungs in the ladder-shaped structure shown above. DNA and RNA generally contain four types of bases: cytosine (C), thymine (T), adenine (A), and guanine (G). Pet. App. 2a.[4] Each rung is composed of two bases, and the bases organize themselves in a predictable fashion—C goes with G, and A goes with T. As a result, one polynucleotide chain will pair, or "hybridize," with a complementary chain composed of complementary bases. *Id.* at 3a. If, for instance, one had a chain AATTCCGG, its complementary chain would be TTAAGGCC. As with the order of letters in this sentence, it is the order of bases in DNA that convey information. This information is called the DNA's "sequence." Due to the predictable fashion in which DNA strands pair, the sequence of one DNA chain can be derived from its complementary chain, like a photographic print from a negative.

It is often desirable to determine whether a test sample contains a particular DNA sequence—for instance, to identify the presence of a gene that predicts a higher risk of a certain cancer. This can be done by creating a "probe" composed of a sequence of nucleotides, which will hybridize with the test sample if a complementary nucleotide sequence is present. To assist in determining whether such hybridizing has occurred, a detectable "label" is attached to the probe.

---

[3] RNA generally exists in a single-stranded form. Like DNA, however, a single strand of RNA can pair with a complementary strand. CAFC JA 7526.

[4] In RNA, uracil replaces thymine as the complementary base to adenine. Pet. App. 2a-3a.

The probe is introduced into the test sample; hybridizing (if any) occurs; any unhybridized material is removed; and, if the probe hybridized with the test sample, the label should be detectable in the sample. This process is illustrated in the diagram reproduced at Pet. App. 81a.

The patents at issue here concern nucleotide labels. Pet. App. 4a-5a.[5] The patents (which share a common specification) explain that the label can be attached directly to a probe via the nitrogenous base of a nucleotide. The label also can be attached to the probe through an intermediate "linkage group." It is this limitation of the patent concerning linkage groups that gives rise to the indefiniteness issue in this case. *Id.* at 4a-5a, 10a-11a. The patent claims at issue do not specify any particular linkage group or groups to use. Rather, the linkage group can be any chemical structure that does not "'interfer[e] substantially'" with the detection probe's function. *Id.* at 4a-5a.[6] The patent also does not define how much interference is "substantial."

---

[5] *See* U.S. Patent Nos. 5,476,928, 5,449,767, and 5,328,824. Specifically, the claims of the three patents are directed to a nucleotide compound, modified with a detectable label, that can be used as a detection probe; or to a method of using such a nucleotide compound as a detection probe.

[6] Specifically, these patents claim a linkage group that does "not interfer[e] substantially with the characteristic ability of said compound to hybridize with said nucleic acid or of A to be detected" ('824 patent col. 31, ll. 31-34); "does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to hybridize with a nucleic acid and does not substantially interfere with formation of the signaling moiety or detection of the detectable signal" ('767 patent col. 31, ll. 2-7); and does "not interfere[e] substantially with detection of A." ('928 patent col. 30, ll. 29-30).

III. PROCEEDINGS BELOW

A. In a complaint filed in the United States District Court for the District of Connecticut, Enzo Biochem, Inc., Enzo Life Sciences, Inc., and Yale University (collectively "Enzo") sued Applera for patent infringement. On October 12, 2006, the district court construed the patents' disputed claim terms. CAFC JA 32-66. Among other things, the district court construed the functional claim limitations "not interfering substantially with" and "does not substantially interfere."[7] *Id.* at 42-44. Adopting Enzo's proposed construction, the court determined that this functionality applied to both hybridization and detection; under the construction, "'the linkage group neither substantially interferes with the ability of the compound to hybridize with the nucleic acid nor substantially interferes with the ability of A to be detected.'"[8] Pet. App. 52a; see also CAFC JA 44.

The district court granted summary judgment to Applera, holding that the asserted claims are invalid because they are indefinite. The court's ruling focused on the "substantially interfere" limitation, concluding that the "specifications neither set forth how one would gauge substantial interference, nor delimit

---

[7] A "functional claim limitation" defines something by what it does or does not do, "rather than by what it is." U.S. Dep't of Commerce, *Manual of Patent Examining Procedure* 2173.05(g) (8th ed. rev. 2010).

These terms appear in claims 1, 42, and 48 of the '767 patent, CAFC JA 182-85; claim 1 of the '824 patent, *id.* at 161-62, and claims 1 and 2 of the '928 patent, *id.* at 202-03.

[8] Although the Federal Circuit *sua sponte* modified the district court's construction as to one of the three patents, *see* Pet. App. 13a, the modification did not alter the construction of "not interfering substantially," and the construction of that critical phrase was not challenged on appeal.

the threshold at which interference with the procedure prevents [the claimed] method from being implemented." Pet. App. 60a. The court explained that

> substantial interference has thus been left to the experimenter to determine the conditions under which detection and hybridization either succeeds or fails. Although the patent expresses a term of degree ("substantial interference"), expert testimony has shown the term to be an illusory yardstick which, if permitted to stand, would sweep all successful hybridization and detection into the ambit of the patents' coverage, while excluding any unsuccessful procedures ....

Id.

The district court independently granted summary judgment to Applera on the ground that the asserted claims of the '767, '824 and '928 patents were invalid under 35 U.S.C. § 102 as anticipated by prior art. Pet. App. 61a-73a.

B. The Federal Circuit reversed, concluding that the asserted claims were sufficiently definite. It reiterated its established standard that "[i]f a claim is indefinite, the claim, by definition, cannot be construed." Pet. App. 10a (citing *Honeywell Int'l, Inc.* v. *ITC*, 341 F.3d 1332, 1342 (Fed. Cir. 2003)). The court found it significant that although the claims do not define "substantially," nor specify how to measure what amount of interference would be "substantial," "[t]he claims in this case provide *at least some guidance* as to how much interference will be tolerated." *Id.* at 14a.

The court found "some guidance" in various "examples" of linkage groups identified in the patents. For instance, in each patent, one dependent claim (not asserted in this litigation as a basis for infringement)

showed a linkage group with a particular structure. Pet. App. 14a-15a. The court reasoned that one could "presume that" this structure "will perform [the] function required of that structure" in the asserted, independent claim. *Id.* at 14a. The court did not address or conclude whether the use of this structure established the boundaries of the claim, nor did the court of appeals modify the claim construction to do so.

Next, and to similar effect, the court noted that "[t]he specification provides additional examples of suitable linkage groups, including some criteria for selecting them." Pet. App. 15a. The court did not conclude that these "examples" establish either a floor or ceiling for measuring how much interference is "substantial." This also was true of the "criteria for selecting" linkage groups. The first criterion was simply that a linkage group could "'withstand all experimental conditions to which normal nucleotides and polynucleotides are routinely subjected.'" *Id.* Second, the court noted the specification's reference to experiments in which melting temperature was used as a proxy for interference. *Id.* at 15a-16a. Two experiments using different probes were reported as producing acceptable results. Neither was identified as establishing an outer boundary of what constitutes substantial interference. *Id.*

Finally, the court cited to the patents' prosecution history to identify eight examples of "specific linkage groups that ... did not substantially interfere with hybridization or detection." Pet. App. 16a. The court did not address, much less decide, whether these linkage groups establish the outer boundaries of the claimed invention.

As noted above, the claims preclude substantial interference with both "hybridization" and "detection."

Turning to detection, the court held the "substantial interference" limitation not indefinite for "most of the same reasons discussed in connection with 'hybridization.'" Pet. App. 18a. The court again cited the eight examples of linkage groups described in the prosecution history. It reasoned that, if testing a potentially infringing product revealed detection "using the exemplary linkage groups," then "a person of ordinary skill would understand that a different linkage group ... likewise does not 'substantially interfere' with ... detection." *Id.* at 19a.

C. The Federal Circuit denied Applera's petition for panel rehearing and rehearing en banc. Pet. App. 75a. Judge Plager dissented, and would have granted panel rehearing. *Id.* at 75a-79a. He began by harshly criticizing the law of indefiniteness as it has developed in the Federal Circuit:

> Despite the varying formulations that this court has used over the years in describing its 'indefiniteness' jurisprudence ..., the general conclusion from our law seems to be this: if a person of ordinary skill in the art can come up with a plausible meaning for a disputed claim term in a patent, that term, and therefore the claim, is not indefinite.

Id. at 75a. The result is the evisceration of the notice function at the heart of the patent system:

> The corollary derived from this understanding is that if several persons of ordinary skill come up with competing but plausible interpretations of a disputed term—as is typically the case with competing "expert witnesses" in patent infringement litigation—the problem is not one of an inherently ambiguous and potentially indefinite claim term, but rather the problem becomes

> simply one of picking the "right" interpretation for that term. Since picking the "right" interpretation—claim construction—is a matter of law over which this court rules, and since the view of the trial judge hearing the case is given little weight, so that the trial judge's view on appeal becomes just a part of the cacophony before this court, it is not until three court of appeals judges randomly selected for that purpose pick the "right" interpretation that the public, not to mention the patentee and its competitors, know what the patent actually claims.

Id. at 76a-77a (footnote omitted).

In contrast to the approach adopted by the Federal Circuit, Judge Plager explained, the PTO is "taking steps to give the statutory requirement real meaning." Pet. App. 77a. He quoted a "rare precedential opinion" of the Board of Patent Appeals (BPAI), which expressly rejected the Federal Circuit's interpretation of the statute. *Id.* at 77a-78a. The BPAI has held that in reviewing patent applications, "'if a claim is amenable to two or more plausible claim constructions, the USPTO is justified in requiring the applicant to more precisely define the metes and bounds of the claimed invention by holding the claim unpatentable under 35 U.S.C. § 112, second paragraph, as indefinite.'" *Id.* at 78a (quoting *Ex parte Miyazaki*, 2008 WL 5105055, at *5).

Judge Plager went on to explain that, "if the public notice function of the patent law is to be honored, claim terms must particularly point out and distinctly claim the subject matter of the invention. In my view, this court's definiteness doctrine could go considerably further in promoting that objective than it currently does, with the not inconsequential benefit of shifting the focus from litigation over claim con-

struction to clarity in claim drafting." Pet. App. 78a-79a. Simply and starkly put: "It is time for us to move beyond sticking our fingers in the neverending leaks in the dike that supposedly defines and figuratively surrounds a claimed invention. Instead, we might spend some time figuring out how to support the PTO in requiring that the walls surrounding the claimed invention be made of something other than quicksand." *Id.* at 79a.

REASONS FOR GRANTING THE PETITION

The Federal Circuit's decisions interpreting the statutory requirement of definiteness have departed from the statutory text and are inconsistent with this Court's precedent. As this Court has explained, the definiteness requirement serves the essential function of ensuring that the public will have clear notice of the boundaries of a claimed invention. Only when there is such clarity can the public determine with confidence what area is reserved to the patentee.

The Federal Circuit's test does not satisfy the statute's purpose. According to that court, a claim is indefinite only if it cannot be construed at all or is "insolubly ambiguous." The scope of a monopoly should not be measured with so indeterminate a yardstick. The statute requires affirmative certainty about the scope of a claim, but the Federal Circuit in stark contrast requires only a slight lack of uncertainty—or, as the Federal Circuit put it here, "some guidance" as to what is off-limits.

By contrast, the PTO applies a more rigorous interpretation of the statute, rejecting a claim as indefinite if it is subject to two or more plausible constructions. The agency has expressly declined to follow the Federal Circuit's interpretation of the statute. This Court's review is warranted to resolve this funda-

mental conflict, and to correct the Federal Circuit's departure from the text of the Patent Act.

I. THE FEDERAL CIRCUIT HAS DEPARTED FROM THE TEXT OF § 112 AND THIS COURT'S PRECEDENTS CONSTRUING IT.

A. The Statutory Language Requires That Patent Claims Be Defined With Particularity And Distinctness.

It is a fundamental requirement of federal patent law that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112 ¶ 2. This Court has emphasized for more than a century that a patent claim must state with specificity the boundaries of the domain that it would seek to monopolize. "The claim is a statutory requirement, prescribed for the very purpose of making the patentee define precisely what his invention is ...." *White* v. *Dunbar*, 119 U.S. 47, 52 (1886). Accordingly, "[t]he statutory requirement of particularity and distinctness in claims is met only when they clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." *United Carbon*, 317 U.S. at 236; accord *General Electric*, 304 U.S. at 369 ("claimed inventions, improvements and discoveries ... require *precise descriptions* of the new characteristic for which protection is sought"); see also *The Incandescent Lamp Patent*, 159 U.S. 465, 475 (1895) (a patent "'should state the component parts of the new manufacture claimed *with clearness and precision*'"); *Merrill*, 94 U.S. at 573 ("[T]he patent law ... leave[s] no excuse for ambiguous language or vague descriptions.").

This specificity serves multiple essential goals. It is necessary to "inform the public during the life of the patent of the limits of the monopoly asserted, so that it may be known which features may be safely used or manufactured without a license and which may not." *Permutit*, 284 U.S. at 60. This is because "[t]he [patent] monopoly is a property right; and like any property right, its boundaries should be clear. This clarity is essential to promote progress, because it enables efficient investment in innovation. A patent holder should know what he owns, and the public should know what he does not." *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 730-31 (2002); see also *Merrill*, 94 U.S. at 573 ("The public should not be deprived of rights supposed to belong to it, without being clearly told what it is that limits these rights.").

Conversely, allowing uncertain claim language undermines the patent system's fundamental goal of encouraging innovation: "A zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field." *United Carbon*, 317 U.S. at 236. Such uncertainty therefore confers an unreasonable benefit on patent owners, at the expense of the public:

> The limits of a patent must be known for the protection of the patentee, the encouragement of the inventive genius of others and the assurance that the subject of the patent will be dedicated ultimately to the public. The statute seeks to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their rights.

General Electric, 304 U.S. at 369 (footnote omitted). In addition, clarity in claim-drafting "enable[s] courts

to determine whether novelty and invention are genuine." *United Carbon*, 317 U.S. at 236. The looseness of the Federal Circuit's standard over the years has encouraged patent draftsmen to be less rather than more clear, as this uncertainty itself confers substantial benefits to the patentholder—it keeps competition away, and makes infringement litigation more expensive for those intrepid enough to test the limits of an existing patent.

B. The Federal Circuit Requires Only That Patent Claims Not Lack Total Ambiguity.

1. The Federal Circuit has created a separate test that is unfaithful to these core principles. A claim is statutorily "definite," the Federal Circuit repeatedly has held, if it is "capable of" or "amenable to construction." *E.g.*, *Source Search Techs. LLC* v. *LendingTree LLC*, 588 F.3d 1063, 1076 (Fed. Cir. 2009); *Ultimax Cement Mfg. Corp.* v. *CTS Cement Mfg. Corp.*, 587 F.3d 1339, 1352 (Fed. Cir. 2009); *Young* v. *Lumenis, Inc.*, 492 F.3d 1336, 1346 (Fed. Cir. 2007); *Honeywell*, 341 F.3d at 1338; *Exxon Research & Eng'g Co.* v. *United States*, 265 F.3d 1371, 1376-80 (Fed. Cir. 2001); see Pet. App. 10a (claim is indefinite if it "cannot be construed"). This rule is erroneous for multiple reasons, and this Court should grant review to bring the Federal Circuit into conformity with the statute and this Court's decisions.

As an initial matter, this standard disregards the reality of claim construction. The mere fact that a claim has been construed does not mean that it cannot be indefinite. During the process of claim construction, a district court does its utmost to interpret and give content to disputed claim terms. But not every claim term will thereby be clarified. And, where particular terms within a claim are unclear, a

court sometimes will construe them with a bare synonym, or not at all, sometimes leaving the question of definiteness for another day. In this case, for instance, the district court construed the claim terms using the phrase "not interfer[e] substantially" with a synonym: "neither substantially interferes." Pet. App. 52a; see also CAFC JA 44. It gave the term no further detail or content, and took this approach at the behest of Enzo, which itself recognized that indefiniteness could result: "If the defendants want to raise an issue with respect to validity at a later date, that's perfectly fine. In fact, the Court should faithfully interpret 'substantially interfering,' and if it's indefinite, then we'll have to live with that." CAFC JA 1644-47.

More fundamentally, the Federal Circuit's indefiniteness standard is by its terms radically different than the statutory requirement. Indeed, the two approaches are nearly opposite. Section 112 imposes an affirmative requirement of "particular[ity]" and "distinct[ness]," which this Court holds requires "clear[]" distinctions," and "precis[ion]." *Supra* at 16-18. Under the Federal Circuit's "capable of construction" jurisprudence, however, a claim is definite so long as it is merely not "insolubly ambiguous." See, *e.g.*, *Honeywell Int'l Inc.* v. *United States*, 609 F.3d 1292, 1301-02 (Fed. Cir. 2010); *Power-One, Inc.* v. *Artesyn Techs., Inc.*, 599 F.3d 1343, 1348 (Fed. Cir. 2010); *Ultimax*, 587 F.3d at 1352.

That lesser standard requires nothing like "particularity" or "precision." Under Federal Circuit law, claim terms "are insolubly ambiguous," and thus indefinite, "only if they provide *no guidance* to those skilled in the art as to the scope of" the invention. *Power-One*, 599 F.3d at 1348; compare Pet. App. 14a (holding the claims at issue here not indefinite be-

cause they "provide at least some guidance as to how much interference will be tolerated"). Thus, as Judge Plager explained, a claim will be held definite "if a person of ordinary skill in the art can come up with a plausible meaning for a disputed claim term." Pet. App. 75a (citing cases). In case after case, the Federal Circuit has held that definiteness requires only a bare modicum of detail. If a reviewing court can put together any construction of the claim terms, the Federal Circuit holds, they necessarily are not indefinite. *See Bd. of Regents* v. *BENQ Am. Corp.*, 533 F.3d 1362, 1368 n.4 (Fed. Cir. 2008) ("As we have been able to discern a construction for the term 'syllabic element,' we reject BENQ's argument that this term is indefinite."). A claim is indefinite only where an accused infringer is entirely unable to ascertain "'*any* reasonable meaning'" of the term. *Young*, 492 F.3d at 1346; *Ultimax*, 587 F.3d at 1352; *Datamize LLC* v. *Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005).

The Federal Circuit's test subverts the statutory notice function. If definiteness only requires some plausible construction, then there can be no notice, because the public will not be given reasonable certainty in advance of its rights. Indeed, the scope of such a patent claim is necessarily uncertain until litigation is finally completed, which is only after the parties' experts and even disagreeing Federal Circuit judges have had their say. Pet. App. 76a-77a (Plager, J., dissenting). But cf. *United Carbon*, 317 U.S. at 236 ("A zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field.").

In short, the Federal Circuit's bare-bones requirement is miles removed from the standard articulated

in the statute, and is distinctly at odds with this Court's emphasis that claim language must provide the public with certainty—not merely "some guidance"—about the scope of a patent in order to achieve the statute's essential notice function. See *General Electric*, 304 U.S. at 369 ("The statute seeks to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their rights.").

2. That the basic notice function has passed by the wayside in the Federal Circuit is clear from a line of cases in which that court has held claims definite based on the existence of nothing more than mere examples of what the patent is meant to cover—regardless whether the examples permit one to determine the actual *boundaries* of the claim.

Thus, in *Exxon Research*, the court found a claim using the term "for a period sufficient" to be definite, even though the patent did not "quantify the 'period sufficient' limitation by reference to any specific period or range of periods." 265 F.3d at 1378. The claim was not indefinite, the court held, because one of skill in the art could look to an example of a "period sufficient" that was described in the patent's specification. *Id.* at 1378-79. It was enough that the public could see at least one use of the language that was within the scope of the claim. See also, *e.g.*, *Hearing Components, Inc.* v. *Shure Inc.*, 600 F.3d 1357, 1367 (Fed. Cir. 2010) (finding the claim term "readily installed and replaced by a user" to be not indefinite because "the written description gives a clear example of a wax guard that is 'readily installed and replaced by a user'"); *Kinetic Concepts, Inc.* v. *Blue Sky Med. Group, Inc.*, 554 F.3d 1010, 1022 (Fed. Cir.) (claim term "selected stage of healing" not indefinite because the patent's specification "provides several

examples of selected stages of healing"), *cert. denied*, 130 S. Ct. 624 (2009).

Here, the Federal Circuit's ruling on indefiniteness depended principally on such examples. *Supra* at 11-13; see Pet. App. 14a-16a. For instance, the court focused on "eight specific linkage groups that Enzo declared did not substantially interfere with hybridization or detection." Pet. App. 16a. But the functional language used in the claims encompasses an infinitely larger group of chemicals—which was made clear by the specification's identification of choices of bonds that might be included in the chemical structure—and these examples do not circumscribe the limits of what structures could be used.

Providing a few examples from a vast category of potential choices identified in a patent's specification does not satisfy the statutory notice function. They do not mark the boundaries of the claims, not least of all because such examples do not limit the scope of the claims. See, *e.g.*, *Fuji Photo Film*, 386 F.3d at 1106. Rather, examples in the specification are simply illustrative of the claimed invention. At most, they therefore serve to identify particular instances of products, methods or the like that would infringe if unlicensed. So while examples may provide "some guidance" as to the meaning of the claim terms, Pet. App. 14a, they do not demarcate the metes and bounds of the invention, nor the area that remains free for experimentation—much less do they define those boundaries with particularity, clarity or precision.[9]

---

[9] As a corollary to its rule that a claim cannot be indefinite if it has been construed, the Federal Circuit holds (and reaffirmed here) that the defenses of indefiniteness and anticipation are mutually exclusive: "If a claim is indefinite, the claim, by defini-

II. THE FEDERAL CIRCUIT'S INTERPRETATION OF § 112 CONFLICTS WITH THE PTO'S.

As Judge Plager explained in his dissent, the PTO has expressly declined to follow the Federal Circuit's test. Rather than limiting indefiniteness to claims that are "insolubly ambiguous," the agency rejects any claim term that is subject to "two or more plausible constructions." As the Board of Patent Appeals and Interferences has explained:

> [W]e employ a lower threshold of ambiguity when reviewing a pending claim for indefiniteness than those used by [the Federal Circuit]. In particular, rather than requiring that the claims are insolubly ambiguous, we hold that if a claim is amenable to two or more plausible claim constructions, the USPTO is justified in requiring the applicant to more precisely define the metes and bounds of the claimed invention by holding the claim unpatentable under 35 U.S.C. § 112, second paragraph, as indefinite.

Ex parte Miyazaki, 2008 WL 5105055, at *5. This conflict alone merits this Court's review: The agency charged with issuing patents has expressly rejected the statutory test employed by the Federal Circuit, and the agency and the court are committed to these disparate standards. Because the Federal Circuit has exclusive jurisdiction over patent cases, a conflict with another regional court of appeals is unlikely, but

---

tion, cannot be construed. Without a discernable claim construction, an anticipation analysis cannot be performed." Pet. App. 10a. This reasoning is flatly illogical. Even if the edges of a patent's claims are insufficiently precise to meet the statutory requirement of definiteness, the claim may be anticipated by prior art that falls clearly within the limits of those fuzzy outer boundaries.

this conflict between the Federal Circuit and the PTO is equally intolerable. Cf. *Keystone Bridge Co.* v. *Phoenix Iron Co.*, 95 U.S. 274, 278 (1877) ("the courts have no right to enlarge a patent beyond the scope of its claim as allowed by the Patent Office").

To be sure, the PTO has attempted to explain the divergence between these standards by suggesting that it may be appropriate to judge patent applications by a different standard than issued patents. *Ex parte Miyazaki*, 2008 WL 5105055, at *4-5. However, both the PTO and the Federal Circuit are interpreting and applying the same statutory language, which cannot and should not be subject to two different meanings. Neither patent applicants, nor those who might compete with them, should be put in the middle of the tug-of-war created by the PTO and the Federal Circuit's competing standards. Such disparate interpretations are inconsistent with the fundamental principle that statutes must be applied consistently in keeping with their plain text, see, *e.g.*, *Jimenez* v. *Quarterman*, 129 S. Ct. 681, 685 (2009), and with the constitutional goal of uniformity in patent law, *Bonito Boats*, 489 U.S. at 162. Notably, the PTO typically interprets other statutory invalidity doctrines in similar fashion to the Federal Circuit—including other doctrines arising under § 112.[10]

---

[10] The PTO and the Federal Circuit employ the same tests for novelty, obviousness, written description and enablement, among others. *Compare, e.g.*, *Ariad Pharms., Inc.* v. *Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (affirming the "'fairly uniform standard'" for assessing the written description requirement of § 112 ¶ 1 articulated in earlier precedent), *and ALZA*, 603 F.3d at 943 (assessing enablement requirement of § 112 ¶ 1), *with Ex parte Kubin*, 83 U.S.P.Q.2d 1410, 1415-17 (B.P.A.I. 2007) (assessing enablement and written description requirements of § 112 ¶ 1), *aff'd*, 561 F.3d 1351 (Fed. Cir. 2009).

Even if there were some justification for the disparate standards on indefiniteness, it would be appropriate to call for the views of the Solicitor General. This is so not only because of the conflicting standards noted above, but also because the United States has questioned the Federal Circuit's interpretation of the definiteness requirement. In an amicus brief filed last year in a case being reheard en banc in the Federal Circuit, to which both the Department of Justice and the PTO Solicitor's Office were signatories, the United States noted that,

> although the statute demands that the claims "particularly point[] out and distinctly claim[] the subject matter which the inventor regards as his invention," the [Federal Circuit] has construed this requirement to require little more than that the claims not be "insolubly ambiguous." *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001). *Cf. United Carbon v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942) (interpreting same language under the 1870 Act to require that the claims "clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise").[11]

This interpretation of the statute, the United States wrote in a marked understatement, is "at a minimum, not compelled by the text of the Patent Act." U.S. Br. at 28.

---

[11] Br. of the United States as Amicus Curiae on Rehearing En Banc in Support of Respondent at 28-29, *Ariad Pharm., Inc.* v. *Eli Lilly & Co.*, No. 2008-1248 (Fed. Cir. filed Nov. 19, 2009), *available at* http://patentdocs.typepad.com/files/amicus-brief---usa.pdf (hereinafter "U.S. Br.") (first two alterations in original).

This Court should grant the petition in order to resolve this conflict, or at a minimum it should ask the Solicitor General to provide the views of the United States on this important question of federal law, which is central to virtually every patent that is issued by the PTO or reviewed by the Federal Circuit.

III. THE DECISION BELOW IS A GOOD VEHICLE FOR RESOLVING THESE ISSUES.

The Federal Circuit's decision in this case vividly illustrates just how far the Federal Circuit has departed from the statutory language and the notice considerations underlying it. The decision below articulates and depends upon the test that is at the root of many of the problems in the Federal Circuit. Pet. App. 10a ("If a claim is indefinite, the claim, by definition, cannot be construed."). The decision below also illustrates more broadly the lax attitude toward indefiniteness that broadly prevails in the Federal Circuit. Far from focusing on the language of the statute or even core concerns of notice, the Federal Circuit stated here that the claims could be considered definite merely because they "provide at least *some guidance* as to how much interference will be tolerated." *Id.* at 14a. It is no accident that Judge Plager chose this case as the occasion to announce that the emperor has no clothes.

First, the decision below repeatedly relies on examples from the patent specification in support of its conclusion that the claims provide "some guidance." But these examples do not mark the boundaries of what is claimed. They are not used in the independent claims, and do not limit the patent's scope; the court of appeals cited, for instance, examples of linkage groups identified in the specification and in the prosecution history. It even relied on examples that appear in dependent claims which are, by definition,

of narrower scope than the independent claims that were asserted in the litigation. *E.g.*, Pet. App. 14a ("A person of ordinary skill would presume that a structure recited in a dependent claim will perform a function required of that structure in an independent claim."); *supra* at 11-12 (describing dependent claims).

Highlighting the lack of meaningful guidance provided even by the narrower dependent claims, elsewhere in its opinion the Federal Circuit observed that there were an "infinite variety of linkage groups" having this "'more preferred'" structure, and even the linkage groups that it earlier had cited as providing "some guidance" would not necessarily perform the function required by the claims. Pet. App. 24a. In short, this case squarely presents the extraordinary situation in which the Federal Circuit has permitted data points to substitute for boundaries, contrary to the statutory requirement of particularity and distinctness.

Second, the patent claims that are at issue here contain functional claim limitations, which this Court has taken up more than once in evaluating definiteness.[12] As here, such claims are susceptible to being drafted very broadly, and the resulting uncertainty about the claims' scope means that a potential infringer would have to undertake "elaborate experimentation" after already having infringed in order even to determine whether it had infringed. *Holland*

---

[12] *E.g.*, *Holland Furniture Co.* v. *Perkins Glue Co.*, 277 U.S. 245, 257 (1928) ("[o]ne attempting to use or avoid the use of Perkins' discovery as so claimed and described functionally could do so only after elaborate experimentation"); *see General Electric*, 304 U.S. at 371 ("the inventor ... uses conveniently functional language at the exact point of novelty"); *see also United Carbon*, 317 U.S. at 233-34 (considering functional claims).

Furniture Co. v. *Perkins Glue Co.*, 277 U.S. 245, 257 (1928).

This case well illustrates the problem. In order to "determine the exact level of detection achieved by the applicants using their exemplary linkage groups," Pet. App. 19a, could require millions of tests to evaluate every single molecule created using Applera's products. This is because, on the Federal Circuit's theory, whether a specific linkage group satisfies the "substantial interference" limitation depends on the "binding strength" of the DNA strand to which it is attached. *Id.* at 18a. That, in turn, will "depend on the length and sequence of the strand." *Id.* Because any change on the molecular level in the length or sequence of a strand could impact the degree of interference (and therefore infringement), the Federal Circuit's analysis means that the way to determine infringement is to test the binding strength of every DNA strand and compare it to the examples in the patent. Testing on this scale, by itself impractical if not impossible, is complicated still further by the fact that these molecules are created not by Applera but by its customers, typically in their own premises and long after they purchased the products. This regime is flatly incompatible with this Court's admonition that the statute requires claims to provide certainty about "the limits of the monopoly asserted, so that it may be known which features may be safely used or manufactured without a license and which may not." *Permutit*, 52 U.S. at 60.

Finally, this case illustrates how the laxity of the Federal Circuit's standard encourages patent owners to exploit the ambiguity surrounding the limits of their exclusive rights. Here, Enzo employed two technical experts who offered differing interpretations of what was required by the claim limitation in

question—a broad interpretation by one expert for infringement, and a narrower one by another for patent validity. One of the experts even conceded that under his interpretation, the claim terminology "'may mean different things to different people.'" See Pet. App. 57a (district court relying on this statement in holding the claims invalid). By adopting its atextual standard, the Federal Circuit has created an incentive for patent owners to adopt expansive or inconsistent interpretations of their patents, safe in the knowledge that the risk of a finding of indefiniteness is remote. This state of affairs epitomizes the "zone of uncertainty" against which this Court has warned.

In sum, this case paradigmatically illustrates the multiple problems that have infected the Federal Circuit's indefiniteness decisions. No other questions of fact or law risk hindering this Court's review of the Federal Circuit's indefiniteness ruling. The case is well-positioned for this Court's review.

CONCLUSION

For the foregoing reasons, this Court should grant the petition for a writ of certiorari.

Respectfully submitted,

NICHOLAS GROOMBRIDGE
JENNIFER H. WU
WEIL, GOTSHAL & MANGES LLP
767 Fifth Avenue
New York, NY 10153
(212) 310-8000

ANTON J. BOKAL
ALAN W. HAMMOND
KURTIS D. MACFERRIN
LIFE TECHNOLOGIES CORP.
850 Lincoln Centre Dr.
Foster City, CA 94404
(650) 554-3410

CARTER G. PHILLIPS*
ERIC A. SHUMSKY
RACHEL TOWNSEND
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, DC 20005
(202) 736-8000
cphillips@sidley.com

TACY F. FLINT
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, IL 60603
(312) 853-7000

JOHN M. WHEALAN
12 Sunnyside Road
Silver Spring, MD 20910
(202) 994-2195

Counsel for Petitioner

*Counsel of Record

September 23, 2010

APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS
FEDERAL CIRCUIT

No. 2009-1281

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., AND YALE UNIVERSITY,
Plaintiffs-Appellants,

v.

APPLERA CORP. AND TROPIX, INC.,
Defendants-Appellees.

March 26, 2010

Before MICHEL, *Chief Judge*, PLAGER, and LINN, *Circuit Judges*.

LINN, *Circuit Judge*.

Enzo Biochem, Inc., Enzo Life Sciences, Inc., and Yale University (collectively, "Enzo") appeal the grant of summary judgment by the U.S. District Court for the District of Connecticut in favor of Applera Corp. and Tropix, Inc. (collectively, "Applera") that all asserted claims of U.S. Patents No. 5,328,824 ("the '824 patent"), No. 5,449,767 ("the '767 patent"), and No. 5,476,928 ("the '928 patent") are invalid as either indefinite or anticipated, and that U.S. Patent No. 5,082,830 ("the '830 patent") is not infringed. *Enzo Biochem, Inc. v. Applera Corp.*, No. 3:04-CV-929 (D.Conn. Mar. 5, 2009). Because we conclude that the

claims of the '824 and '767 patents are not indefinite, and because we find genuine issues of material fact as to anticipation, we reverse the district court's summary judgment of invalidity of those two patents. Although we find that the '928 patent is not indefinite, we affirm the district court's judgment of anticipation as to that patent. Because the district court correctly construed the claims of the '830 patent, under which the patent is not infringed, we affirm the judgment of noninfringement. The case is remanded.

BACKGROUND

Enzo's patents-in-suit are directed to various techniques for labeling and detecting nucleic acids, such as DNA and RNA. To put the analysis in context, we begin with a brief discussion of the basic technology and vocabulary related to this case and undisputed by the parties.

I. Basic Technology and Vocabulary

DNA and RNA are composed of a series of units, called "nucleotides." Each nucleotide is composed of a nitrogenous base, a pentose sugar, and a phosphate group. The phosphate group of one nucleotide forms a covalent bond with the pentose sugar of an adjacent nucleotide, thereby linking the nucleotides along a "sugar-phosphate backbone." Aside from linking the nucleotide units into a polynucleotide strand, the sugar-phosphate backbone provides structural support for the nitrogenous bases. The bases fall into two categories: pyrimidines and purines. Pyrimidines include cytosine ("C"), thymine ("T"), and uracil ("U"). Purines include adenine ("A") and guanine ("G"). DNA contains the bases adenine, thymine, cytosine, and guanine; RNA also includes adenine, cytosine, and

guanine, but contains the base uracil in place of thymine. Two strands of DNA or RNA having complementary bases will bind, or "hybridize," to form a double-stranded complex, or "hybrid," which is held together by hydrogen bonds between complementary bases. In DNA, adenine on one strand binds to thymine on the other; in RNA, adenine binds to uracil; and in both DNA and RNA, cytosine binds to guanine. The process of forming a double-stranded hybrid is called "hybridization." The reverse process, resulting in two separate strands, is called "denaturation."

Because hybridization occurs in a predictable manner between complementary strands, it is possible to detect the presence of a nucleic acid of interest in a sample. For example, a chemical entity, called a "label," can be attached to or incorporated into a nucleic acid strand of a known sequence, called a "probe," which will hybridize with a complementary sequence of interest, called a "target." Once the probe is hybridized with the target, a detectable signal is generated either from the label itself (referred to as "direct detection") or from a secondary chemical agent that is bound to the label (referred to as "indirect detection"). If a signal is detected from the sample after all unhybridized probes have been removed, detection of the signal implies the presence of a target in that sample.

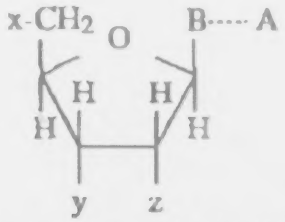
Labeling of nucleic acids has been accomplished using a variety of chemical entities. For example, with radioactive labels, an isotope of hydrogen (^{3}H), phosphorous (^{32}P), or carbon (^{14}C) is substituted for a non-radioactive atom within the probe, and the isotope is then detected using a radiation detector. But radioactive labels have drawbacks. As explained in the '824, '767, and '928 patents, radioactive labels

are "potentially hazardous," "expensive to purchase and use," and "often very unstable." '824 patent col.1 ll.34-45.[1]

To avoid these drawbacks, the inventors of the patents-in-suit developed a series of nucleotide probes that do not rely on traditional radioactive labels. The '824, '767, and '928 patents are directed to these developments and all claim priority to an application filed on April 17, 1981. The '830 patent issued from an application filed on February 26, 1988 and is directed to improvements over some of the probes claimed in the earlier patents.

II. The '824, '767, and '928 Patents

In general, the claims of the '824, '767, and '928 patents are directed to a "compound" (whose structure is depicted below), or a method of using that compound as a detection probe. In this compound, a nitrogenous base "B" is covalently attached, either directly or through a "linkage group" (represented by the dotted line), to a chemical moiety "A."



The "linkage group" is not recited in the independent claims in structural terms. Rather, the linkage group is recited functionally as "not interfering substantially" with both hybridization and detection

[1] Because the '824, '767, and '928 patents share a common specification, we shall cite the '824 patent when referencing the common specification.

('824 and '767 patents) or simply detection ('928 patent). *See* '824 patent col.31 ll.31-34 ("said linkage group not interfering substantially with the characteristic ability of said compound to *hybridize* with said nucleic acid or of A to be *detected*" (emphases added)); '767 patent col.31 ll.2-7 ("a linkage group that does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to *hybridize* with a nucleic acid and does not substantially interfere with formation of the signalling moiety or *detection* of the detectable signal" (emphases added)); '928 patent col.30 ll.29-30 ("said linkage group not interfering substantially with *detection* of A" (emphasis added)). The specification describes the function of the linkage group as follows:

> [I]t is generally preferred that the chemical linkage include an olefinic bond at the α-position relative to B . . . . [Which] serves to hold the moiety A away from the base when the base is paired with another in the well known double-helix configuration. This permits interaction with polypeptide to occur more readily, thereby facilitating complex formation. Moreover, single bonds with greater rotational freedom may not always hold the moiety sufficiently apart from the helix to permit recognition by and complex formation with polypeptide.

'824 patent col.8 ll.54-68.

The chemical moiety A is the label that facilitates detection. In claim 1 of the '824 and '767 patents, moiety A "comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing a detectable signal." In claim 1 of the '928 patent, moiety A "represents at least three carbon atoms and an indicator molecule

selected from the group consisting of fluorescent dyes, electron-dense reagents, enzymes which can be reacted with a substrate to produce a visually detectable reaction product, and radioisotopes."

The symbols "x," "y," and "z" represent, variously, one of the following: hydrogen, hydroxyl, or one or more components of the sugar-phosphate backbone.

III. The '830 Patent

The later-filed '830 patent contains claims to both a compound and a method of detection using that compound. The claimed compound is a nucleotide labeled with "at least one non-radioactive moiety directly or indirectly attached to each of the 5' and 3' end nucleotides thereof." '830 patent col.13 ll.63-65, col.14 ll.58-61. The 5' and 3' positions are locations on a pentose sugar: the 5' end is the so-called "left" end of the polymer; the 3' end is the so-called "right" end of the polymer. In the method claim, a "target" strand is contacted under hybridization conditions with both (i) a "probe" strand having 5' and 3' labels and (ii) a "preformed detectable molecular complex." *Id.* col.14 ll.53-64. Detection is accomplished by "detecting any hybridized complexes." *Id.* col.14 ll.65-66.

IV. Proceedings Below

On June 7, 2004, Enzo sued Applera for infringement of six patents, four of which are here on appeal.[2] The asserted claims of the four patents on appeal are: claims 1, 18, 19, 21, 26, 28, 32, and 33 of the '824 patent; claims 1, 2, 8, 11, 13, 42, 46-51, 67, 68, and 70 of the '767 patent; claims 1 and 2 of the '928 patent; and claims 1, 12, and 18 of the '830 patent.

---

[2] The unappealed patents are U.S. Patents No. 4,711,955 and No. 4,994,373.

The district court issued a claim construction ruling on October 12, 2006. *Enzo Biochem, Inc. v. Applera Corp.*, No. 04-929, 2006 WL 2927500 (D.Conn. Oct. 12, 2006) ("*Claim Construction*"). With regard to the linkage group in each of the '824, '767, and '928 patents, the district court construed the "not interfering substantially" language to mean that "the linkage group neither substantially interferes with the ability of the compound to hybridize with the nucleic acid nor substantially interferes with the ability of A to be detected." *Id.* at *6. With regard to the moiety A, the district court found the differing claim language of the '824, '767, and '928 patents to be relevant to whether A constitutes the whole or merely a portion of the entity that produces a detectable signal. More specifically, with regard to the '824 and '767 patents, the district court held that "A may be a part of or the entire signalling moiety," and therefore adopted Enzo's proposed construction that "A comprises at least three carbon atoms and is one or more parts of a signalling moiety, which includes, in some instances, the whole signalling moiety." *Id.* at *4. By contrast, the district court held that the plain language of the '928 patent "precludes a construction where A is the entire [indicator] molecule," and therefore adopted Applera's proposed construction that "A must have at least three carbon atoms and an indicator molecule selected from the group consisting of (i) fluorescent dyes, (ii) electron-dense reagents, (iii) enzymes which can be reacted with a substrate to produce a visually detectable reaction product, or (iv) radioisotopes." *Id.* at *5. Finally, as to the "non-radioactive moiety" of the '830 patent, because the claims call for the use of a "detectable molecular complex," the district court construed "non-radioactive moiety" to mean "a moiety that is utilized in indirect detection, i.e., a moiety

that can be detected with a preformed detectable molecular complex." *Id.* at *11.

Enzo conceded that under the district court's construction it could not prove infringement of the '830 patent. Based on this concession, the district court granted summary judgment of noninfringement of the '830 patent on August 7, 2007. Applera then moved for summary judgment of invalidity of all asserted claims of the '824, '767, and '928 patents based on: (1) lack of written description under 35 U.S.C. § 112, ¶ 1; (2) lack of enablement under 35 U.S.C. § 112, ¶ 1; (3) indefiniteness under 35 U.S.C. § 112, ¶ 2; and (4) anticipation under 35 U.S.C. § 102.

On September 6, 2007, the district court denied Applera's summary judgment motion as to lack of written description and enablement, but granted the motion as to indefiniteness and anticipation. *Enzo Biochem, Inc. v. Applera Corp.*, No. 3:04-CV-929, 2007 WL 2669025 (D.Conn. Sept. 6, 2007) ("*Summary Judgment*"). With regard to indefiniteness, the district court held that the "not interfering substantially" language in the asserted claims of all three patents is indefinite because "[t]he specifications neither set forth how one would gauge substantial interference, nor delimit the threshold at which interference with the procedure prevents [the claimed] method from being implemented." *Id.* at *12. Alternatively, the district court found these same claims to be anticipated by at least one of three prior art references.[3] In concluding that there was no genuine issue

---

[3] The three prior art references are: Hiroshi Kasai et al., *Specific fluorescent labeling of 7-(aminomethyl)-7-deazaguanosine located in the anticodon of tRNA^{Tyr} isolated from E. coli mutant*, 7 Nucleic Acids Res. 231 (1979) ("Kasai"); Alfred Pingoud et al., *Fluoresceinylthiocarbamyl-tRNA^{Tyr}: a useful derivative of tRNA^{Tyr}*

of material fact that the prior art taught a linkage group that did "not substantially interfere" with hybridization and detection, the district court observed that "[a]lthough this Court has determined that the 'substantially interfere' language in the ['824, '767, and '928 p]atents is the basis for their invalidity, interpretation of the phrase for purposes of anticipation does not affect the invalidity ruling." *Id.* at *13. Thus, on summary judgment, all asserted claims of the '824, '767, and '928 patents were held invalid as either indefinite or anticipated.

The district court entered final judgment with respect to all six patents on March 5, 2009. Enzo appeals the final judgment with respect to the '824, '767, '928, and '830 patents. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

"A determination that a patent claim is invalid for failing to meet the definiteness requirement in 35 U.S.C. § 112, ¶ 2 is a legal question reviewed *de novo*." *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1344 (Fed. Cir.2007). "Because a patent is presumed to be valid, the evidentiary burden to show facts supporting a conclusion of invalidity is one of clear and convincing evidence." *Id.* at 1345. "We review a district court's grant of summary judgment de novo, reapplying the standard applicable at the district court." *Id.* "While anticipation is a question of fact, 'it may be decided

---

(E.coli) for physiochemical studies, 4 Nucleic Acids Res. 327 (1977) ("Pingoud"); J.G.J. Bauman, *Cytochemical Detection of Specific Nucleic Acid Sequences Development and Application of In Situ Hybridisation Methods for Fluorescence Microscopy* (doctoral thesis publ. Drukkerji J.H. Pasmans b.v. 's-Gravenhage, Netherlands (1980)) ("Bauman").

on summary judgment if the record reveals no genuine dispute of material fact.'" *Leggett & Platt, Inc. v. VUTEk, Inc.*, 537 F.3d 1349, 1352 (Fed.Cir.2008) (quoting *Golden Bridge Tech., Inc. v. Nokia, Inc.*, 527 F.3d 1318, 1321 (Fed.Cir.2008)). Summary judgment is appropriate "if the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed.R.Civ.P. 56(c)(2).

I. The '824, '767, and '928 Patents

Enzo challenges the district court's grant of summary judgment that all asserted claims of the '824, '767, and '928 patents are invalid in the alternative—as indefinite, but if not indefinite, then invalid as anticipated. As a preliminary matter, we observe that a claim cannot be both indefinite and anticipated. A determination that a claim is anticipated involves a two-step analysis: "the first step requires construing the claim," and "[t]he second step in the analysis requires a comparison of the properly construed claim to the prior art . . . . " *Power Mosfet Techs., LLC v. Siemens AG*, 378 F.3d 1396, 1406 (Fed.Cir.2004). If a claim is indefinite, the claim, by definition, cannot be construed. Without a discernable claim construction, an anticipation analysis cannot be performed. *See Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1342 (Fed.Cir.2003) (vacating finding of infringement entered after claims were properly held to be indefinite).

A. Indefiniteness

On appeal, Enzo first argues that the district court incorrectly determined that the "not interfering substantially" language in the '824, '767, and '928 patents

is indefinite. In Enzo's view, the specifications provide specific examples of linkage groups that do not substantially interfere with hybridization and detection, as well as general criteria for selecting suitable linkage groups. Moreover, Enzo asserts that the specification provides a test for measuring the degree of interference, namely, comparing the thermal denaturation profile (i.e., melting temperature) of a modified polynucleotide with that of an unmodified polynucleotide.

Applera responds that the district court correctly determined that the "not interfering substantially" language is indefinite, arguing that nothing in the patents explains how to measure "interference" or how to determine whether it is "substantial." Because even a minor alteration of a single nucleotide may have profound effects on the ability of a DNA strand to hybridize, depending on the length and sequence of the strand, Applera argues that identical linkage groups may cause interference in some strands but not in others, thus rendering the claims hopelessly ambiguous.

We agree with Enzo that the claims are not indefinite. "Indefiniteness requires a determination whether those skilled in the art would understand what is claimed. To make that determination, we have explained that '[i]n the face of an allegation of indefiniteness, general principles of claim construction apply.'" *Young*, 492 F.3d at 1346 (quoting *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1348 (Fed.Cir.2005)). "In that regard, claim construction involves consideration of primarily the intrinsic evidence, *viz.*, the claim language, the specification, and the prosecution history." *Id.* When a "word of degree" is used, the court must determine whether

the patent provides "some standard for measuring that degree." *Seattle Box Co., Inc. v. Indus. Crating & Packing, Inc.*, 731 F.2d 818, 826 (Fed.Cir.1984). Similarly, when a claim limitation is defined in "purely functional terms," a determination of whether the limitation is sufficiently definite is "highly dependent on context (e.g., the disclosure in the specification and the knowledge of a person of ordinary skill in the relevant art area)." *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1255 (Fed.Cir.2008).

Because the claim language of the '824 and '767 patents differs from that of the '928 patent with regard to "hybridization" and "detection," we address these two terms separately.

1. Hybridization

The claims of the '824 and '767 patents provide that the linkage group must not substantially interfere with both hybridization and detection: '824 patent col.31 ll.31-34 ("said linkage group not interfering substantially with the characteristic ability of said compound to *hybridize* with said nucleic acid or of A to be *detected*" (emphases added)); '767 patent col.31 ll.1-7 ("a linkage group that does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to *hybridize* with a nucleic acid and does not substantially interfere with formation of the signalling moiety or *detection* of the detectable signal" (emphases added)). By contrast, the claims of the '928 patent provide only that the linkage group must not substantially interfere with detection: "said linkage group not interfering substantially with *detection* of A." '928 patent col.30 ll.28-30 (emphasis added). The district court, however, adopted an identical construction for all three patents that refers to both hybridization and detection: "the linkage group

neither substantially interferes with the ability of the compound to *hybridize* with the nucleic acid nor substantially interferes with the ability of A to be *detected*." *Claim Construction*, 2006 WL 2927500, at *6 (emphases added).

As a preliminary matter, we see no basis to read a "hybridization" requirement into the claims of the '928 patent. Nothing in the claims refers to hybridization, and neither the specification nor the prosecution history contains a clear disclaimer or a contrary definition regarding the "not interfering substantially" language that would require us to read such a requirement into the claims. The applicants knew how to claim a linkage group that does not substantially interfere with hybridization, as they did in the '824 and '767 patents, but specifically omitted that language from the claims of the related '928 patent. We therefore modify the construction of this limitation with regard to the '928 patent to read: "the linkage group does not substantially interfere with the ability of A to be detected."

With regard to the '824 and '767 patents, the term "hybridization" has a definite meaning. The district court correctly understood the term to mean "the binding of two separate, complementary strands of nucleic acids to form nucleic acid hybrids." *Id.* at *1 n. 1. The ambiguity, in the district court's view, was that a person of ordinary skill would not understand whether a linkage group interferes with hybridization "substantially."

We begin with the language of the claims. The word "substantially," when used in a claim, can denote either language of approximation or language of magnitude. *See Deering Precision Instruments, LLC v. Vector Distrib. Sys., Inc.*, 347 F.3d 1314, 1323 (Fed.Cir.2003).

As used in the phrase "not interfering substantially," the word "substantially" denotes language of magnitude because it purports to describe *how much* interference can occur during hybridization, i.e., an insubstantial amount of interference. *See Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1031 (Fed.Cir.2002) ("[T]he phrase 'substantially below' signifies language of magnitude, i.e., not insubstantial."). The claims in this case provide at least some guidance as to how much interference will be tolerated. A dependent claim in both patents specifies that the linkage group has a particular structure (-CH=CH-CH_2-NH-). *See* '824 patent col.32 ll.66-68; '767 patent col.31 ll.38-40. A person of ordinary skill would presume that a structure recited in a dependent claim will perform a function required of that structure in an independent claim. *See AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1242 (Fed.Cir.2003) ("Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend."). Thus, it may be presumed that the term "not interfering substantially" in the independent claims allows for at least as much interference as that exhibited when the linkage group has the structure specified in the dependent claims.[4]

---

[4] Of course, if this particular embodiment is inoperable, because a linkage group having the structure -CH=CH-CH_2-NH- entirely precludes hybridization, then the basis for invalidity would be a lack of enablement, not indefiniteness. *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1382 (Fed.Cir.2001) (stating that inoperable embodiments present "an issue of enablement, and not indefiniteness"); *Miles Labs., Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed.Cir.1993) ("The invention's operability may say nothing about a skilled artisan's understanding of the bounds of the claim.").

The specification provides additional examples of suitable linkage groups, including some criteria for selecting them. After stating generally that the linkage group "may include any of the well known bonds including carbon-carbon single bonds, carbon-carbon double bonds, carbon-nitrogen single bonds, or carbon-oxygen single bonds," the specification goes on to note that "[i]t is even more preferred that the chemical linkage group be derived from a primary amine, and have the structure -CH_2-NH-, since such linkages are easily formed utilizing any of the well known amine modification reactions." '824 patent col.8 ll.54-58, col.9 ll.1-5. Moreover, one of the "essential criteria" of a modified polynucleotide noted in the specification is that "the linkage that attaches the probe moiety should withstand all experimental conditions to which normal nucleotides and polynucleotides are routinely subjected, e.g., extended hybridization times at elevated temperatures, phenol and organic solvent extraction, electrophoresis, etc." *Id.* col.6 l.29, col.7 ll.3-8.

The specification also teaches that the polynucleotides' "thermal denaturation profiles and hybridization properties" can be used to measure the degree to which a linkage group interferes with hybridization. *Id.* col.18 ll.61-62. Because hybridization occurs via hydrogen bonding between complementary bases, any interference in this bonding will result in weaker intermolecular forces and thus a lower melting temperature (T_m) of the hybrid. For example, the specification states that a DNA strand was modified by substituting every thymidine residue of the strand with a biotinyl-nucleotide. The resultant hybridization exhibited by the modified DNA strand was reported to be acceptable: "the T_m is *only* 5 °C less than that of the unsubstituted control." *Id.* col.19 ll.5-8 (emphasis

added). A similar test was performed on poly d(A-bioU), in which every base pair contained a bio-dUMP residue. This modified polynucleotide showed a significantly lower T_m than the unsubstituted control, yet its hybridization was still deemed acceptable: "Although the T_m . . . is 15 °C lower than the poly d(A-T) control, the *degree of cooperativity and the extent of hyperchromicity* observed both during denaturation and renaturation *were the same* for the two polymers." *Id.* col.19 ll.9-14 (emphases added). Thus, as a general guideline, when a linkage group is incorporated into a DNA strand having a length and sequence similar to those used in the specification, a decrease in T_m of up to 5 °C implies that the linkage group does not "substantially interfere" with hybridization, and a decrease of up to 15 °C is acceptable if the degree of cooperativity and the extent of hyperchromicity are the same for the modified and unmodified strands.

The prosecution history of these patents is also helpful. Before the U.S. Patent and Trademark Office ("PTO"), Enzo overcame an indefiniteness rejection over the "not interfering substantially" language by submitting a declaration under 37 C.F.R. § 1.132, which was signed by its vice president, Dr. Engelhardt ("Engelhardt Declaration"), listing eight specific linkage groups that Enzo declared did not substantially interfere with hybridization or detection. Among the named linkage groups was $-CH=CH-CH_2-NH-$ (the same group recited in the patents' dependent claims) and $-NH-(CH_2)_6-NH-$ (a new group that is not found in the specification and which contains only single bonds). J.A. 4320. Based on this submission, the examiner withdrew the indefiniteness rejection.

Because the intrinsic evidence here provides "a general guideline and examples sufficient to enable a

person of ordinary skill in the art to determine [the scope of the claims]," *In re Marosi*, 710 F.2d 799, 803 (Fed.Cir.1983), the claims are not indefinite even though the construction of the term "not interfering substantially" defines the term without reference to a precise numerical measurement, *see Young*, 492 F.3d at 1346 (holding that a word of degree was definite, even without a numerical claim construction); *Exxon*, 265 F.3d at 1381 (same); *Marosi*, 710 F.2d at 803 (same); *In re Mattison*, 509 F.2d 563, 565 (CCPA 1975) (same). When deciding whether a particular linkage group is or is not "substantially" interfering with hybridization within the meaning of the district court's construction, a person of ordinary skill would likely look to the thermal denaturation profiles and hybridization properties (including T_m) of the modified nucleotide, to see whether they fall within the range of exemplary values disclosed in the intrinsic evidence. *See Young*, 492 F.3d at 1346 (stating that a figure in the specification "provides a standard for measuring the meaning of the term 'near,'" even without a numerical claim construction); *Exxon*, 265 F.3d at 1380 (stating that a "period sufficient," recited in the claim, can be ascertained by performing activity checks).

Contrary to Applera's assertion, the fact that the binding strength of a DNA strand may vary, based on the length and sequence of the strand, does not mean that the choice of a linkage group will "depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention," as in *Datamize*, 417 F.3d at 1350. In *Datamize*, the invention was directed to a computer interface screen with an "aesthetically pleasing look and feel." *Id.* at 1344-45. The patentee sought a construction of the term "aesthetically pleasing" that depended solely on

the subjective opinion of the person selecting features to be included on the interface screen. Nothing in the intrinsic evidence provided any guidance as to what design choices would result in an "aesthetically pleasing" look and feel. *Id.* at 1352. The claims were held indefinite because the very same interface screen may be "aesthetically pleasing" to one user but not to another.

Here, by contrast, the binding strength of a DNA strand will depend on the length and sequence of the strand, not on the subjective opinion of the particular chemist performing the hybridization. This is because, under a given set of experimental conditions, a DNA strand of a given length and sequence will have a fixed, measurable denaturation profile, which can be compared with the examples in the specification to determine whether interference with hybridization is substantial. The claims are not indefinite simply because the binding strength of a DNA strand will vary based on the strand's length and sequence. *See Young*, 492 F.3d at 1346 (holding claim definite even though "the size of the appendage and the amount of skin required to be incised will vary from animal to animal based on the animal's size").

Thus, we hold that the claim language regarding "hybridization" is not indefinite.

2. Detection

With regard to "detection," we agree with Enzo that the claims are not indefinite for most of the same reasons discussed in connection with "hybridization." The eight linkage groups listed in the Rule 132 declaration were said not to "interfere[ ] with the ability of biotin in an oligo- or polynucleotide probe of this invention to form a detectable complex with one

of avidin, streptavidin or antibodies to biotin or iminobiotin." J.A. 4318. According to the specification, when biotin is used as the moiety A, the resultant complexes can be detected "by means of conventional detection techniques." '824 patent col. 18 ll.4-6. So long as moiety A can be detected within the level of detection achieved by the applicants using the exemplary linkage groups disclosed in the intrinsic evidence, a person of ordinary skill would understand that a different linkage group (one that is not disclosed in the intrinsic evidence) likewise does not "substantially interfere" with the detection of moiety A. The claims are not indefinite even if some experimentation is required to determine the exact level of detection achieved by the applicants using their exemplary linkage groups. *See Exxon*, 265 F.3d at 1379 ("Provided that the claims are enabled, and no undue experimentation is required, the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite.").

* * *

For the foregoing reasons, we conclude that the "not interfering substantially" language in the '824, '767, and '928 patents is not indefinite.

B. Anticipation

The district court granted Applera's motion for summary judgment that (1) Kasai anticipates the asserted claims of the '824 and '767 patents, (2) Pingoud anticipates the asserted claims of the '767 patent, and (3) Bauman anticipates the asserted claims of the '928 patent. On appeal, Enzo argues that none of the references disclose a "linkage group" that does not substantially interfere with hybridiza-

tion, and that the testimony of its expert, Dr. Sherman, was sufficient to create a genuine issue of material fact.

In moving for summary judgment on an issue as to which Applera bore the burden of persuasion, Applera supported its motion with detailed claim charts showing where each and every claim limitation is disclosed in the prior art, and an expert declaration explaining how the prior art meets those limitations under the district court's claim construction. *See Saab Cars USA, Inc. v. United States*, 434 F.3d 1359, 1369 (Fed.Cir.2006) (party with the burden of persuasion on an issue must "provide evidence sufficient, if unopposed, to prevail as a matter of law"); 11 James Wm. Moore, Moore's Federal Practice § 56.13[1] (3d ed. 2009) ("[I]f the movant has the burden of persuasion on an issue, the movant must make a stronger claim to summary judgment by introducing supporting evidence that would conclusively establish movant's right to a judgment after trial should nonmovant fail to rebut the evidence."). With respect to the "linkage group" limitation, two of Applera's prior art references (Kasai and Pingoud) employ a $-CH_2-NH-$ linkage group, which arguably belongs to the set of linkage groups disclosed in the patents-in-suit as "even more preferred" embodiments. '824 patent col.9 ll.1-5 ("It is even more preferred that the chemical linkage group be derived from a primary amine, and have the structure $-CH_2-NH-$, since such linkages are easily formed utilizing any of the well known amine modification reactions."). Moreover, all three of Applera's references, on their face, report the ability to detect the presence of moiety A. If unopposed, this evidence would entitle Applera to judgment as a matter of law. We therefore agree with

the district court that Applera carried its initial burden of making a prima facie showing of anticipation.

"When a motion for summary judgment is properly made and supported, an opposing party may not rely merely on allegations or denials in its own pleading; rather, its response must—by affidavits or as otherwise provided in this rule—set out specific facts showing a genuine issue for trial." Fed.R.Civ.P. 56(e)(2). The requirement that the nonmovant must set forth "specific facts" means that "[m]ere denials or conclusory statements are insufficient" to survive summary judgment. *Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd.*, 731 F.2d 831, 836 (Fed.Cir.1984). The standard on this issue is the same in the Second Circuit, *see Davis v. New York*, 316 F.3d 93, 100 (2d Cir.2002), which applies in this case "because the issue is a procedural matter not unique to patent law." *Arthur A. Collins, Inc. v. N. Telecom Ltd.*, 216 F.3d 1042, 1048 (Fed.Cir.2000).

After reviewing the material that Enzo submitted in opposition to Applera's summary judgment motion, we conclude that Enzo has raised a genuine issue of material fact as to Kasai and Pingoud sufficient to survive summary judgment of anticipation of the '767 and '824 patents. However, as discussed below, Enzo has failed to raise a genuine issue of material fact with respect to Bauman and the '928 patent.

1. Kasai

With respect to Kasai, Enzo offered the declaration of its expert, Dr. Sherman, who stated that Kasai's "aminomethyl group [(-CH_2-NH-)] would not provide sufficient rigidity to prevent significant interference with hybridization of a complementary polynucleotide. Indeed, one would predict based on the flexibility of

this functional group and the concomitant high degree of motion, there would be significant interference due to free rotation about the single bonds." Sherman Decl. ¶ 44. This is in contradistinction to a linkage group including a carbon-carbon double bond, which presumably would be sufficiently rigid to prevent significant interference with hybridization, because the bound elements would not be free to rotate about their axes and sterically interfere at the hybridization site.

During prosecution, Enzo submitted the Engelhardt Declaration, which listed eight suitable linkage groups that did not substantially interfere with hybridization or detection. Seven included a carbon-carbon double bond, and one, -NH-$(CH_2)_6$-NH-, consisted entirely of single bonds. Applera argues that Dr. Sherman's declaration cannot be credited because it conflicts with Dr. Engelhardt's declaration that an all-single-bond linkage group was suitable. *See Cleveland v. Policy Mgmt. Sys. Corp.*, 526 U.S. 795, 806, 119 S.Ct. 1597, 143 L.Ed.2d 966 (1999) ("The lower courts . . . have held with virtual unanimity that a party cannot create a genuine issue of fact sufficient to survive summary judgment simply by contradicting his or her own previous sworn statement (by, say, filing a later affidavit that flatly contradicts that party's earlier sworn deposition) without explaining the contradiction or attempting to resolve the disparity."). Applera would have us agree with the district court that Dr. Sherman's declaration did not raise a genuine issue of material fact because he "offer[ed] no support, experimental, literary, or otherwise, for [his] assertion" that Kasai would substantially interfere, and that Applera is entitled to summary judgment of anticipation. *See Summary Judgment*, 2007 WL 2669025, at *13.

Applera's argument ignores the standard for summary judgment, which requires that Dr. Sherman's declaration be viewed in a light most favorable to Enzo. *See Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 149 F.3d 1309, 1315 (Fed.Cir.1998) ("In deciding whether summary judgment was appropriate, we view the evidence in a light most favorable to the party opposing the motion with doubts resolved in favor of the opponent.") (internal citations omitted). Viewing the declaration in a light most favorable to Enzo requires that Dr. Sherman's explanation be read as limited to the specific one-carbon aminomethyl group disclosed in Kasai and not as a sweeping condemnation of single bonds or an unyielding requirement of double bonds. *See* Sherman Decl. ¶ 44 ("[T]he *aminomethyl group* would not provide sufficient rigidity to prevent significant interference with hybridization.") (emphasis added). Dr. Sherman's statement that the aminomethyl group disclosed in Kasai would substantially interfere and Dr. Engelhardt's statement that a six-carbon diamine group would not are not inconsistent, particularly when viewed in a light most favorable to Enzo, as it must be.

Moreover, at least two characteristics of a linkage group contribute to its character as interfering with hybridization or not: the nature of the bonds (i.e., single or double) and the length of the chain. In his declaration, Dr. Sherman chose to focus on the first (the lack of a double bond) in explaining why Kasai would substantially interfere. The '824 patent indicates the preferability of a double bond in the linkage group. '824 patent col.8 ll.58-65 ("[I]t is generally preferred that the chemical linkage include an olefinic [(i.e., double)] bond . . . . [This] serves to hold the moiety A away from the base when the base is paired with another in the well known double-helix

configuration."). *See also* Engelhardt Decl. Ex. A (seven of eight examples incorporate a double bond, including a short three-carbon chain linkage group). However, while Dr. Sherman did not discuss it, the '824 patent also recognizes that the *length* of the linkage group impacts hybridization and detection. *See* '824 patent col.8 ll.65-68 ("Moreover, single bonds with greater rotational freedom may not always hold the moiety *sufficiently apart from the helix* to permit recognition by and complex formation with [a] polypeptide.") (emphasis added). It is elementary stereochemistry that a longer linkage group could hold the moiety farther from the hybridization site than a shorter one. Viewed with this understanding of the technology, the declaration of Dr. Engelhardt cannot be said to obviate the genuine issue of material fact raised by Dr. Sherman's declaration.

Applera also argues that because Kasai's -CH_2-NH- linkage group is within the group of "even more preferred" embodiments, it cannot substantially interfere. However, there are an infinite variety of linkage groups "derived from a primary amine, [with] the structure -CH_2-NH-," *see* '824 patent col.9 ll.1-15, which suggests that not every "even more preferred" linkage group would satisfy the not substantially interfering element. Further, Enzo argues that the "even more preferred" language is properly read as describing a subset of the preferred embodiments—i.e., those with carbon-carbon double bonds at the α-positition—such that the most preferred embodiments have both a carbon-carbon double bond at the α-position, *and* are derived from a primary amine and include a -CH_2-NH- group. The examples in the specification of the most preferred embodiment have both a carbon-carbon double bond at the α-position and an aminomethyl group. '824 patent col. 9 ll.8-16.

Enzo's reading is reasonable, and should have been credited on summary judgment.

For the reasons stated, we reverse the district court's grant of summary judgment of invalidity of the asserted claims of the '824 and '767 patents as anticipated by Kasai.

2. Pingoud

Applera presents two arguments that Pingoud anticipates the '767 patent. First, it relies on a statement by its expert, Dr. Kricka, that "Pingoud was able to detect the label without apparent difficulty, so to the extent Enzo contends that the mere ability to detect a label is sufficient to satisfy this claim limitation presumably they would not dispute that Pingoud satisfies this claim limitation as well." Kricka Decl. ¶ 84, App. A at 60. Second, Applera repeats its argument that Pingoud belongs to the set of compounds described as "even more preferred" in the patents.

Neither argument is sufficient to sustain summary judgment. On its face, Pingoud notes that there was substantial interference with hybridization. Pingoud at 327 ("Codon-anticodon interaction . . . is severely affected by the [fluorescent labeling] modification."). "Codon-anticodon interaction" is indicative of hybridization, and "severely affected" suggests substantial interference. Dr. Sherman recognized this, and, unlike Dr. Kricka, opined that "there would be substantial interference" by the compound disclosed in Pingoud. Sherman Decl. at ¶¶ 61-62. Thus there is a genuine issue of material fact as to whether the Pingoud linkage group substantially interferes with hybridization.

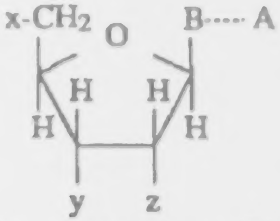
We reject Applera's "most preferred embodiment" argument for the same reasons discussed above in regard to Kasai.

Therefore, we reverse the district court's grant of summary judgment of anticipation of the asserted claims of the '767 patent based on Pingoud.

3. Bauman

Enzo's argument with regard to Bauman is insufficient to raise a genuine issue of material fact. Bauman employs a mercury glutathione linkage group to attach moiety A to base B. However, instead of attaching the linkage group before hybridization, Bauman first performs hybridization and then attaches the linkage group, along with moiety A, to the hybrid. Once attached, moiety A is detected by fluorescence. Because Bauman performs hybridization *before* labeling the polynucleotide, Enzo argues that Bauman cannot anticipate the asserted claims of the '928 patent. In Enzo's view, the claims "require that the linkage group not interfere *after* the label is attached." Reply Br. of Pl.-Appellants 23. We disagree.

First, the claims of the '928 patent are directed to a product, not a process. More specifically, independent claims 1 and 2 are simply directed to a "compound" having the structure:



It is irrelevant, for purposes of anticipation, what method is used, much less what order of steps is used, to attach both moiety A and the linkage group

to base B. *See In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir.1985) ("The patentability of a product does not depend on its method of production.").

Second, as we have already explained, the "not interfering substantially" language in the '928 patent is silent as to hybridization. All that is required of this particular linkage group is that it not substantially interfere with the ability of A to be detected. Enzo does not dispute that Bauman discloses a linkage group that does not substantially interfere with the ability of A to be detected.

Because the district court correctly held that Enzo failed to raise a genuine issue of material fact with respect to Bauman, we affirm the judgment of anticipation as to claims 1 and 2 of the '928 patent.[5]

II. The '830 Patent

The district court construed the term "non-radioactive moiety" in the '830 patent to mean "a moiety that is utilized in indirect detection, i.e., a moiety that can be detected with a preformed detectable molecular complex." *Claim Construction*, 2006 WL 2927500, at *11. Enzo would like the term construed simply to mean "a non-radioactive detection moiety." Thus, under Enzo's proposed construction, the moiety could be utilized in either indirect detection

---

[5] Because Bauman anticipates claims 1 and 2 of the '928 patent under the district court's narrower construction of moiety A, wherein A represents only a portion and not the entirety of the indicator molecule, Bauman would necessarily anticipate these claims if, as Enzo argues, A is broad enough to represent either a portion or the entirety of the indicator molecule. Because it would not change the result in this case, we decline to address Enzo's claim construction argument with regard to moiety A.

(wherein the preformed detectable molecular complex is the thing that generates a detectable signal) or direct detection (wherein the non-radioactive moiety is itself the thing that generates a detectable signal). We agree with the district court's construction.

Claims 1, 12, and 18 are independent claims. Claim 14 is a multiple dependent claim that refers back to claims 1 and 12. The claims recite, with key term emphasized:

> 1. An oligo- or polynucleotide having at least one *non-radioactive moiety* directly or indirectly attached to each of the 5' and 3' end nucleotides thereof.
>
> 12. An oligo- or polynucleotide having at least one *non-radioactive moiety* directly or indirectly attached to each of the 5' and 3' terminal nucleotides external to a target hybridization region of said oligo- or polynucleotide.
>
> 14. A nucleic acid hybridization assay composition comprising an oligo- or polynucleotide of claims 1 or 12, and a preformed detectable molecular complex.
>
> 18. A method for detecting a target nucleic acid sequence in a sample comprising:
>
> rendering the nucleic acid in said sample in single-stranded form;
>
> contacting said single-stranded nucleic acid under hybridizing conditions with (i) an oligo- or polynucleotide probe having at least one *non-radioactive moiety* directly or indirectly attached to each of the 5' and 3' end nucleotides thereof, said probe being capable of hybridizing to said

target nucleic acid sequence, and (ii) a preformed detectable molecular complex; and

detecting any hybridized complexes, thereby detecting the target nucleic acid sequence.

Enzo concedes that the term "non-radioactive moiety" cannot be given its literal meaning (i.e., a molecular substructure not labeled with a radioisotope), since the claims would then encompass any piece of natural DNA, rendering the claims invalid on their face. The district court therefore looked to the specification, which contains no disclosure of direct detection but instead refers to an "analyte-specific moiety" detected using "detectable molecules." '830 patent col.3 ll.41-53. Because all detectable molecules mentioned in the specification are those relating to detection via a "preformed detectable molecular complex," the district court concluded that a "non-radioactive moiety" must be detected via a signal generated from the preformed detectable molecular complex rather than from the moiety itself. On appeal, Enzo faults the district court for equating "non-radioactive moiety" with "analyte-specific moiety," and argues that the specification instead equates "non-radioactive moiety" simply with "labeling" of nucleic acids using "labeling moieties." *Id.* col.1 ll.8-11. But even if a non-radioactive moiety is simply a "label," as Enzo suggests, this still leaves open the question whether the non-radioactive moiety is itself capable of generating a detectable signal or whether the preformed detectable molecular complex is what generates the signal.

The claim language strongly suggests that the non-radioactive moiety serves simply as a binding site for a preformed detectable molecular complex, and that the signal is generated by the complex, not the moiety.

Independent claim 18 is unambiguously limited to indirect detection via "a preformed detectable molecular complex." *Id.* col.14 ll.63-64. If the non-radioactive moiety were itself the thing that generated a detectable signal, then there would be no reason to contact it with the preformed detectable molecular complex, as required in part (ii) of the "contacting" step of claim 18. Moreover, in the last step of this claim, what is detected is "any hybridized *complexes*," not the moiety. *Id.* col.14 l.65 (emphasis added). Thus, at least with regard to claim 18, the "non-radioactive moiety" is a moiety that can be detected with a preformed detectable molecular complex. Enzo has not argued that the "non-radioactive moiety" should have a different meaning in independent claim 18 than in independent claims 1 and 12. Indeed, we have recognized that "claim terms are normally used consistently throughout the patent." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir.2005) (en banc).

Referring to the claim language, Enzo argues that the district court's construction of "non-radioactive moiety" violates the doctrine of claim differentiation. Under this doctrine, "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Id.* at 1315. Because dependent claim 14 adds "a preformed detectable molecular complex" to claim 1, Enzo asserts that the district court's construction of "non-radioactive moiety"—which refers to detection with "a preformed detectable molecular complex"—renders the two claims coextensive. But the district court's construction imposes no requirement that a preformed detectable molecular complex is actually present in claim 1; rather, it simply requires the "non-radioactive moiety"

to be capable of performing a function: "*can* be detected with a preformed detectable molecular complex." *Claim Construction*, 2006 WL 2927500, at *11 (emphasis added). Claim 1, unlike claim 14, is infringed even in the absence of a preformed detectable molecular complex. *See Revolution Eyewear, Inc. v. Aspex Eyewear, Inc.*, 563 F.3d 1358, 1370 (Fed. Cir.2009) (holding that a component of an accused device meets "capable of engaging" limitation even though device is not designed or sold with component in engaging configuration). Because claim 1 is broader than claim 14 under the district court's construction, this case simply does not implicate the doctrine of claim differentiation.

The specification lends no support to Enzo's proposed construction because it contains no disclosure whatsoever of direct detection. This fact alone is not dispositive, of course, because "it is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment—into the claims absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed.Cir.2004). But, as already discussed, the claim language strongly suggests that the non-radioactive moiety must have the capability of being indirectly detected with a detectable molecular complex.

The prosecution history is not to the contrary. Enzo overcame an obviousness rejection by stating:

> Prior to the instantly claimed invention, no mention or suggestion was ever made regarding the attachment (directly or indirectly) of at least one non-radioactive moiety, e.g., biotin or a biotin analogue, to each of the 5' and 3' end nucleotides

> of an oligo- or polynucleotide. Furthermore, no prior art reference ever taught or suggested the possibility of a nucleic acid hybridization assay composition comprising such a *labelled oligo- or polynucleotide and a preformed detectable complex*, e.g., a preformed avidin or streptavidin detectable molecular complex, as defined by the present claims.

J.A. 307 (emphasis added). On appeal, Enzo argues that this statement supports its proposed construction because it equates a "non-radioactive moiety" with a "labeled oligo- or polynucleotide," which in turn suggests that the moiety is simply a "label." But again, the question is how this "label" is detected. The very same sentence that refers to the claimed compound as a "labelled oligo- or polynucleotide" also refers to a "preformed detectable complex," suggesting that detection is accomplished by the latter. Indeed, the unique binding of a biotin moiety with an avidin complex, referenced in this passage, is an example of indirect detection. Moreover, these prosecution statements were made with regard to all rejected claims standing or falling together, and were not directed to any dependent claim reciting a detectable molecular complex as an express limitation of the claim. All of this suggests that the non-radioactive moiety must be capable of indirect detection with a preformed detectable molecular complex. The prosecution history thus tends to undercut, rather than support, Enzo's proposed construction.

For the foregoing reasons, we affirm the district court's construction of "non-radioactive moiety." Because Enzo stipulated that it cannot prove infringement under this construction, we affirm the judgment of noninfringement of the '830 patent.

CONCLUSION

We reverse the district court's grant of summary judgment that the asserted claims of the '824 and '767 patents are invalid as indefinite and anticipated by Kasai and further that the asserted claims of the '767 patent are anticipated by Pingoud. We affirm the judgment that the '928 patent is invalid as anticipated. We affirm the judgment that the '830 patent is not infringed. The case is remanded for further proceedings consistent with this opinion.

APPENDIX B

UNITED STATES DISTRICT COURT
D. CONNECTICUT

No. 3:04cv929 (JBA)

ENZO BIOCHEM, INC. *et al.*,
Plaintiffs,

v.

APPLERA CORP. *et al.*,
Defendants.

Sept. 6, 2007

RULING ON DEFENDANT APPLERA'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY [DOC. # 182]

JANET BOND ARTERTON, U.S.D.J.

Plaintiffs Enzo Biochem, Inc., Enzo Life Sciences, Inc., and Yale University (collectively "Enzo") allege patent infringement under 35 U.S.C. §§ 271, *et seq.* against defendants Applera Corp. ("Applera") and Tropix Inc. ("Tropix") with respect to three of four "Ward Patents," specifically Claims 1, 18, 19, 21, 26, 28, 32, and 33 of U.S. Patent No. 5,328,824 ("'824 Patent"); Claims 1, 2, 8, 11, 13, 42, 46, 47, 48, 49, 50, 51, 67, 68, and 70 of Patent No. 5,449,767 ("'767 Patent"); and Claims 1 and 2 of Patent No. 5,476,928 ("'928 Patent"). (*See* Compl. [Doc. # 1] at 1; Def. Reply

Mem. [Doc. # 224] at 2 n. 1.)[1] Defendant Applera now moves for summary judgment of invalidity as to these Ward patents on grounds of failure to satisfy the written description and enablement requirements of 35 U.S.C. § 112 ¶ 1, failure to satisfy the claim definiteness requirement of 35 U.S.C. § 112 ¶ 2, and anticipation under 35 U.S.C. § 102. For the reasons that follow, defendant Applera's Motion will be GRANTED.

I. *Factual Background*

As set out in the Court's Claim Construction Ruling, the Ward patents disclose a method of non-radioactive labeling for detecting the presence of DNA or RNA in a sample. *See Enzo Biochem, Inc. v. Applera Corp.*, No. 3:04cv929 (JBA), 2006 U.S. Dist. LEXIS 74570 (D.Conn. Oct. 12, 2006) ("Claim Construction Ruling"). This method of labeling is effected via the formation of a complex between hybridized nucleotides and a detectable polypeptide. The Ward Patents, which share a specification, are based on a single application filed April 17, 1981 on behalf of then Yale professor Dr. David Ward and two colleagues. The first Ward Patent, the '955 Patent, *see supra* n. 1, issued in 1981; an overview of the asserted claims is provided below.

A. *'824 Patent*

The '824 Patent, which issued on July 12, 1994, discloses a two-step process by which a probe is hybridized with an analyte and then detected as a means of determining the existence of a particular analyte in the sample. Of the asserted claims of this Patent, independent Claim 1 is representative:

---

[1] Plaintiffs no longer press their claims related to Patent No. 4,711,955 ("'955 Patent").

A method of detecting the presence or absence of a nucleic acid in a sample which comprises the steps of

(a) contacting under hybridizable conditions said sample with at least one compound comprising the structure: [DIAGRAM]

[. . . .]

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing a detectable signal;

wherein B and A are covalently attached directly or indirectly through a linkage group, said linkage group not interfering substantially with the characteristic ability of said compound to hybridize with said nucleic acid or of A to be detected;

wherein if B is 7-deazapurine, A is attached to the 7-position thereof, and if B is pyrimidine, A is attached to the 5-position thereof;

wherein m, n and p are integers, provided that m and p are not simultaneously 0 and provided further n is never 0; and

wherein z represents H- or HO-; and

(b) detecting said compound or compounds so as to detect said nucleic acid.

('824 Patent, Pls. Ex. 6.) Dependent Claims 18, 19, 21, 26, 28, 32, and 33 describe the structure of the A moiety, indicator molecule B, and the nucleic acid disclosed in Claim 1.

B. *'767 Patent*

The '767 Patent issued on September 12, 1995 and discloses a particular nucleotide useful in hybridization. Plaintiffs allege infringement of independent Claims 1, 42, and 48, and numerous dependent claims. Claim 48 is representative:

> An oligo- or polynucleotide containing therein a sugar moiety having the structure: [DIAGRAM]
>
> [. . . .]
>
> wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing a detectable signal; and
>
> wherein B and A are covalently attached directly or through a linkage group that does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to hybridize with a nucleic acid and does not substantially interfere with formation of the signalling moiety or detection of the detectable signal, provided also that if B is a 7- deazapurine, A or the linkage group is attached to the 7-position of the deazapurine, and if B is pyrimidine, A or the linkage group is attached to the 5-position of the pyrimidine.

('767 Patent, Pls. Ex. 5.) Dependent claims 49, 50, 51, 67, 68, and 70 are directed to the structure of the sugar moiety or of A. Independent Claims 1 and 42 share much of the language in Claim 48, except that Claim 1 discloses that the oligo- or polynucleotide contains a "nucleotide" rather than a sugar moiety, and Claim 42 discloses an "oligo- or polynucleotide sequence comprising at least one of a moiety having the structure: -BA."

C. '928 Patent

Issued on December 19, 1995, the '928 Patent discloses a compound useful as a probe to detect the presence of and/or localize specific polynucleotide sequences. Independent Claim 1 is representative:

> A compound useful as a probe for detecting the presence or absence of a nucleic acid, said compound having the structure: [DIAGRAM]
>
> [. . . .]
>
> wherein A represents at least three carbon atoms and an indicator molecule selected from the group consisting of fluorescent dyes, electron-dense reagents, enzymes which can be reacted with a substrate to produce a visually detectable reaction product, and radioisotopes;
>
> wherein B and A are covalently attached directly or through a linkage group, said linkage group not interfering substantially with detection of A;
>
> wherein if B is a purine, A is attached to the 8-position of the purine, if B is a 7-deazapurine, A is attached to the 7-position of the deazapurine, and if B is a pyrimidine, A is attached to the 5-position of the pyrimidine; and
>
> wherein each of x, y and z represents: [DIAGRAM].

('928 Patent, Pls. Ex. 4.) Independent Claim 2, the only other Claim asserted by Enzo, is substantially similar to Claim 1, except that it discloses that "one of x and y represents [DIAGRAM] and the other of x and y is absent or represents -OH or -H" and that "z represents H- or HO-."

The Court's Claim Construction Ruling construed certain terms relevant to the claims on the instant Motion. First, the '824 and '767 Patents were construed to "cover both direct and indirect detection," *Enzo Biochem*, 2006 U.S. Dist. LEXIS 74570 at 9, on the basis that "A comprises at least three carbon atoms and is one or more parts of a signaling moiety, which includes, in some instances, the whole signaling moiety." Second, the terms "linkage group not interfering substantially with" and "linkage group that does not substantially interfere with" in all of the asserted independent claims were construed to mean that "the linkage group neither substantially interferes with the ability of the compound to hybridize with the nucleic acid nor substantially interferes with the ability of A to be detected," *id.* at 16-17.

II. *Summary Judgment and Invalidity Standards*

Summary judgment is appropriate under Federal Rule of Civil Procedure 56(c) when the moving party establishes that there is no genuine issue of material fact to be resolved at trial and that the moving party is entitled to judgment as a matter of law. *See Celotex Corp. v. Catrett*, 477 U.S. 317 (1986). Materiality is determined by the substantive law that governs the case. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). "Where the record taken as a whole could not lead a rational trier of fact to find for the nonmoving party, there is no genuine issue for trial." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986).

"A defendant need not prove a negative when it moves for summary judgment on an issue that the plaintiff must prove at trial. It need only point to an

absence of proof on plaintiff's part, and, at that point, plaintiff must 'designate specific facts showing that there is a genuine issue for trial.'" *Parker v. Sony Pictures Entm't, Inc.*, 260 F.3d 100, 111 (2d Cir.2001), quoting *Celotex*, 477 U.S. at 324.

A patent is presumed valid, as are the individual claims of a patent. 35 U.S.C. § 282. The party claiming invalidity bears "the burden to show the invalidity of the claims by clear and convincing evidence as to underlying facts." *Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1364 (Fed.Cir.1998). This standard demands evidence that proves in the mind of the trier of fact "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Intel Corp. v. Int'l Trade Comm'n*, 946 F.2d 821, 829-30 (Fed Cir.1991) (affirming determination that patent not invalid where "extensive inference" from evidence did not meet the clear and convincing standard).

III. *Discussion*

A. *Written Description Requirement*

The first of defendant's summary judgment grounds is that Patents '824 and '767 are invalid under Patent Act § 112 ¶ 1, which requires that a specification "contain a written description of the invention, and of the manner and process of making and using it, in . . . full, clear, concise, and exact terms," 35 U.S.C. § 112 ¶ 1. According to Applera, although Patents '824 and '767 have been construed by the Court to cover both direct and indirect detection, the specification inadequately describes a system for direct detection.

In order to satisfy the written description requirement, the specification must show that the applicant possessed the invention as of the filing date, *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed.Cir.1991), thus ensuring that "the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification," *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed.Cir.2000). The written description may be accomplished "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed instruction." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed.Cir. 1997). "While it is legitimate to amend claims or add claims to a patent application . . . there must be support for such amendments or additions in the originally filed application." *PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1247 (Fed.Cir. 2002). "The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed.Cir.2005). A claim is not invalidated simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed.Cir.2006).

In contesting whether the specification teaches direct detection, defendant makes several arguments. First, Applera focuses on the "A" moiety, which is defined in the specification as follows:

> A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the

> compound is incorporated into a double-stranded ribonucleic acid, deoxyribonucleic acid duplex, or DNA-RNA hybrid;

'824 Patent 7:26-30.[2] Defendant contends that the specification discusses the "A" moiety as capable of only indirect detection, meaning that direct detection was not possessed by Enzo when the Ward Patents issued, and that the disclosed labels are described in reference to indirect detection.

Applera is correct that the specification repeatedly references "A"'s capability of "forming a detectable complex with a polypeptide ('824 Patent 3:49-50, 5:33-34, 7:26-27, 8:4-5, 11:16-17; 16:66-67), and describes "A" (in the form of disclosed labels biotin, iminobiotin, and various haptens) as "interacting with appropriate antibodies to produce complexes" (*id.* at 8:12-13) or as "coupled to potentially demonstrable indicator molecules" (including the fluorescent dyes fluorscein and rhodamine) to be used in detection of a biotin probe (*id.* at 18:7-17). According to defendant's expert Larry J. Kricka, "[t]he specification repeatedly and exclusively discloses that the 'A' moiety is detected not by itself, but by complexing it with a labeled (and thus detectable) polypeptide to form a complex that generates a detectable signal." (Kricka Decl. [Doc. # 183] ¶ 107.) He observes that "[e]ach disclosure in the specification of 'indicator molecules' explicitly describes such molecules as being coupled to a detector protein—an entity that is used to detect the 'A' moeity—and not to the 'A' moiety itself." (*Id.* ¶ 110.) Plaintiffs respond to these portions of the specification by arguing that because direct

---

[2] Because the specification is identical for all of the Ward Patents, the Court will cite only to the '824 Patent for consistency.

detection methods using fluorescent dyes and other single-component signaling systems were known when the Ward specification was filed, the specification's disclosure of labeled nucleotides suitable for incorporation into polynucleotides is sufficient, and, more importantly, that Example 9 of the specification discloses direct detection.

While Examples 1 through 6 undisputedly disclose only indirect detection methods (Sinden Supplem. Expert Report, Pls. Ex. 3, ¶ 15), Enzo's expert witness Richard R. Sinden opines that Example 9, particularly in the context of Examples 7 and 8, "disclose[s] techniques that involve detection where A is the whole of the signalling moiety" (*id.* ¶ 10). Examples 7 and 8, entitled "Synthesis of NAGE-UTP and NAGE-dUTP," describe the method for synthesizing the linker arm NAGE, which can be attached to UTP and dUTP nucleotides. (*Id.* ¶ 11; '824 Patent at 28-29.) Example 9 sets out "Karyotyping," "Diagnosis of Genetic Disorders," and "Microorganism Detection and Identification" as "Uses of Labeled DNA Sequences." ('824 Patent at 29-30.) Sinden reads Example 9 as invoking the labeling procedures in Examples 7 and 8 and providing for direct detection methods using fluorescent dyes: he interprets the phrase "adding a fluorescent stain to the label" in Example 9 as denoting attachment of a fluorescent dye to the available amine group of the NAGE linker from Examples 7 and 8, and not the addition of biotin with subsequent detection using a linked indicator as in indirect detection Examples 1 through 6. (Sinden Supplem. Expert Report, Pls. Ex. 3, ¶ 13.) Indirect detection using biotin as compatible with Examples 1 through 6 would lead to background interference or distort detection results, Sinden opines. (*Id.* ¶ 15.)

Moreover, Sinden points to Example 9's allowance for "two sets of labels," a condition he claims is specific to the direct detection context. (*Id.* ¶ 16.)

Applera's expert Kricka, in contrast, claims that Example 9 simply elaborates on uses for labeled sequences set out in the preceding eight examples, all of which describe indirect detection methods. He quotes from the karyotyping section of Example 9, and reads it as exclusively describing indirect detection:

> polynucleotides are hybridized with chromosomal deoxyribonucleic acid and the resulting duplexes contact with appropriate polypeptides under suitable conditions to permit complex formation. The polypeptides include detectable moieties so that the location of the complexes can be determined and the location of specific genes thereby fixed.

Id. at ¶ 113, quoting '824 patent at 24:40-50. In addition, Applera further points to a paper published by two of the Ward Patents' inventors, David Ward and Pennina R. Langer-Safer, in 1982 that discloses a method of performing the procedures in Example 9 using only indirect labels, as well as to a 1990 paper by Ward on using multiple probes labeled with different indirect labels to analyze chromosomes. See Pennina R. Langer-Safer, et al., "Immunological method for mapping genes on Drosophila polytene chromosomes," *Proc. Natl. Acad. Sci. USA*, (1982), Pls. Ex. 7; Ann L. Boyle, *et al.*, "Differential distribution of long and short interspersed element sequences in the mouse genome: Chromosome karyotyping by fluorescence *in situ* hybridization," *Proc. Natl. Acad. Sci. USA* (1990), Pls. Ex. 8. Indeed, Sinden recognizes the two-color analysis method

using indirect detection described in the 1990 paper as "one embodiment" of what is contemplated by Example 9 such that "it is possible to carry out the procedures of Example 9 of the Ward patent using an indirect detection system." Apr. 13, 2006 Sinden Dep., Def. Ex. 9, at 127, 128.)[3]

In *Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916 (Fed.Cir.2004), the Federal Circuit affirmed a judgment of invalidity for inadequate written description where the functional description of the invention consisted of a bare assertion that the patent covered "'a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product,'" *id.* at 928, without further narrowing its scope by disclosing "just which peptides, polynucleotides, and small organic molecules have the desired characteristic of selectively inhibiting PGHS-2," *id.* at 927 (internal quotations omitted)(emphasis in origi-

---

[3] That the prosecution histories of the '824 and '767 Patents reveal "A" moieties disclosing only biotin and iminobiotin, indirectly detectable moieties, does not necessarily compel a finding that the patents fail to meet the written description requirement with respect to direct detection, particularly given that the letter defendant sent to the U.S. Patent and Trademark Office ("PTO") protesting issuance of the '767 Patent could be interpreted as reflecting Applera's understanding that the '767 and '824 Patents cover direct detection. (See Letter from Applera's Senior Patent Counsel Stephen C. Macevicz to Assistant Commissioner of Patents Lawrence J. Goffney, Jr., Pls. Ex. 20, at GT008336 ("Nothing in any of the Ward specifications, the prosecution up to 1994, or pending claims up to 1994 give any indication that the invention includes compounds covering DNA sequencing fragments. . . . The only rationale for this claim is to obtain a claim that literally covers DNA sequencing fragments so that the opportunistic patent priorietor can extract royalties or other concessions out of the real industry participants under threats of patent infringement suits.").)

nal). The court found that the language of the specification had cast too wide a net, cautioning that while patent applicants need not provide a step-by-step narrative of reduction to practice, an ordinarily skilled artisan cannot be left with "a vague functional description" which does not fairly delineate the infringing from the non-infringing, *id.* at 926, 927. *See also Lizardtech, Inc. v. Regents of the Univ. of Cal.*, 424 F.3d 1336, 1346 (Fed.Cir.2005) (affirming judgment of invalidity where patent specification recited the procedure by which to manufacture one possible invention purported to be covered by the patent, but where specification was impermissibly vague as to the range of inventions covered thereby).

The facts at bar do not present the Court with such a clear want of specificity. While the text of the specification, which repeatedly discusses the "A" moiety as "forming a detectable complex with a polypeptide, suggests disclosure of only indirect detection, the record contains clashing but reasonable expert interpretations of the meaning of Example 9. Thus, the Court concludes that defendant has not proven by clear and convincing evidence that a skilled practitioner would read the '824 and '767 Patents to disclose *only* indirect detection, and summary judgment on this point is inappropriate.

B. *Enablement*

Next, defendants claim that Ward Patents '824 and '767 are invalid for lack of enablement under Patent Act § 112 ¶ 1, which requires the specification's language to include "such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the [invention]." Applera notes that in an unrelated interference proceeding before the U.S. Patent and Trademark Office ("PTO") on May 3, 2007, concerning a patent outside this case being disputed by Enzo and Applera,[4] Enzo's expert Dr. Bruce A. Roe submitted a declaration asserting that direct labeling was not enabled in any scientific publication until 1985. Since the Ward Patents were available before 1985, including European Patent No. 063879—the European equivalent of the Ward Patents, which was published on November 3, 1982, Ward Eur. Pat.App., Def. Supplem. Ex. 3,—Applera argues that Dr. Roe's opinion amounts to an admission by Enzo that the Ward patents do not enable the direct detection method, and that because the specification does not allow practice of the full scope of the claimed invention without undue experimentation, the Ward Patents are invalid for lack of enablement. Enzo accuses defendants of mischaracterizing Roe's testimony, which they claim pertained only to whether a specific labeling chemistry was actually disclosed in a particular patent, and point out that Roe admitted that he had not exhaustively searched the prior art before testifying.

The interference proceeding in which Roe's declaration was submitted was an *inter partes* PTO administrative proceeding to determine which of multiple entities first invented specific subject matter claimed in competing patents or patent applications. *See* 35 U.S.C. § 135. Claim 14 of the disputed '058 Patent, which is assigned to the California Institute of Technology and exclusively licensed to Applera, sets

---

[4] Specifically, patent 5,821,058 ('058 patent), and allowed patent application 08/486,069.

out a method of DNA sequencing in which polynucleotide fragments are "tagged with a chromophore or fluorophore," that chromophore or fluorophore being a directly detectable label. (Roe Decl., Def. Supplem. Ex. 2, ¶ 21, quoting '058 Patent.) On May 3, 2007, Enzo moved that Caltech be denied the '058 patent's claimed "priority date" of January 16, 1984 on the grounds that the application on which Caltech bases its priority (No. 06/570,973 ("'973 Application")) lacks an enabled embodiment of Claim 14 of the '058 patent, because: "Methods for tagging nucleotides with fluorescent labels to determine the sequence of a polynucleotide were not publicly known until at least 1985." (Enzo Subst. Mot. in Interf. Procdg. 4, Def. Supplem. Ex. 1, at 4.)

In his declaration, Roe opines that a person skilled in the art, prior to 1985, "would not have been able to select the precise reagents, reaction conditions and process steps necessary to achieve a successful coupling of a chromophore or fluorophore from the multitude of possibilities, without at least undue experimentation." (Roe Decl., Def. Supplem. Ex. 2 ¶ 28.) In writing his declaration, Roe "reviewed the scientific literature published from about the late 1970s to about the late 1980s, in the field of DNA sequencing." (*Id.* ¶ 29.) At his deposition, Roe testified that his review of the literature before writing his report included "at least the Langer et al., that's David Ward I think is on that. I'd have to check." (June 12, 2007 Roe Dep., Def. Supplem. Ex. 4, at 116.)[5] When queried about the methods enabled by

[5] With respect to the Langer-Safer/Ward publication that Roe had reviewed (Langer-Safer (1981), see supra) on "enzymatic synthesis of biotin-labeled polynucleotides" (June 12, 2007 Roe Dep., Def. Supplem. Ex. 4, at 116-17), Enzo argues that Kricka's

the plaintiffs' '955 patent, Roe was unsure until given a chance to re-read the patent:

> Q: Let me be more specific, is there anything in this Ward patent that you could point me to that would tell a skilled person how to couple a fluorophore directly to a polynucleotide?
>
> A: Can I take some time to look through the patent?
>
> [. . . .]
>
> Q: Just to confirm, you've had the chance to look through the Ward '955 patent?
>
> A: Yes, I have.
>
> Q: And is there anything in that patent that would teach a person of skill how to directly couple a fluorophore to a polynucleotide? And let me just be clear, when I say directly, I mean by a covalent bond whether through a linker arm or not.
>
> A: No. Thank you for giving me time to look through that.

(*Id.* at 133.) Dr. Roe certified the accuracy of the deposition transcript, and did not submit any amendments or corrections.

The key inquiry is the extent to which the subject matter of Roe's testimony ("coupling a fluorophore or chromophore to the 5' amino of a polynucleotide fragment in a manner suitable for determining the

---

knowledge of this article is irrelevant because it disclosed no example of direct labeling, in contrast to Examples 7, 8, and 9 of the Ward Patents specification. As the same arguments are made here regarding the Examples as in relation to the lack of written description, *supra*, the Court will not restate its analysis.

sequence of the polynucleotide" (Roe Decl., Pls. Supplem. Opp. Ex. 2, ¶ 26)) constitutes direct detection and hybridization. If the coupling testified to by Roe signifies direct detection and hybridization, then Roe's testimony can be taken to mean that detection and hybridization were not enabled before 1985.

In the Court's view, the question of the breadth of Roe's testimony is resolved by his clarification that his interference declaration merely states that "certain coupling chemistry was not known before a certain date" (*id.* at 26) (emphasis added), and that the declaration itself addresses the '973 Application and the "aliphatic amino group at the 5' terminus" (Roe Decl., Pls. Ex. 2, ¶¶ 25, 26, 30, 35, 38). A later declaration by Roe in the same proceeding confirms the conclusion that Roe's denial of enablement in the Ward patents is limited to a particular procedure not at issue in this litigation:

> All the steps for conducting DNA sequencing were known to a person of skill in the art in 1982 except for the step of tagging a polynucleotide fragment with a chromophore or fluorophore in a manner suitable for determining the polynucleotide sequence from the fragments in accordance with the Count.

(Roe Second Decl., Def. Supplem. Reply Ex. 1, ¶ 60.) Moreover, Enzo rightly points out that Applera's own expert Kricka testified and stated in his report on invalidity that direct labeling was known in the field by the time the first Ward patent issued in 1981 (Kricka Expert Report, Pls. Ex. 8, ¶ 30; Kricka Dep., Pls. Ex. 9, at 170), with which assessment Enzo's experts Sinden and Sherman agreed (Sinden Reply Expert Report, Pls. Ex. 7 ¶ 56; Sinden Dep., Pls. Ex.

6, at 46; Sherman Dep., Pls. Ex. 5, at 110). However, as Applera notes, the experts agreed that attachment of fluorescent labels for hybridization was known in 1981, not that the specific method suitable for DNA sequencing was known. (Def. Supplem. Reply at 8.)[6]

As the declaration of Roe is focused on what was known about direct detection in relation to 5' amino coupling in the '058 Patent/'093 Application context, the evidence proffered in support of defendant's enablement ground for invalidity does not compel granting summary judgment.

C. *Claim definiteness*

Applera argues that the Ward Patents are invalid because the term "interfering substantially" does not meet the definiteness requirement of Patent Act § 112 ¶ 2, which demands that patent claims "particularly point[ ] out and distinctly claim[ ] the subject matter which the applicant regards as his invention," 35 U.S.C. § 112 ¶ 2, as understood by one skilled in the art, *Invitrogen Corp. v. Biocrest Mfg.*, 424 F.3d 1374, 1383 (Fed.Cir.2005). The exact words employed in a patent specification are vital, as "claims delineate the scope of the invention using language that adequately notifies the public of the patentee's right to exclude." *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed.Cir.2005). A claim will be rejected for indefiniteness where it "is not sufficiently precise to

---

[6] Plaintiffs also point out that Applera's anticipation argument, see infra, is itself premised on the notion that direct labeling of nucleic acids was known before 1981. *See Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed.Cir.2003) (A patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.").

provide competitors with an accurate determination of the 'metes and bounds' of protection involved." *Ex parte Lyell*, 17 U.S.P.Q.2d 1548, 1550-51 (Bd. Pat.App. & Int.1990). A specification invites a determination of indefiniteness when it "leaves those skilled in the art entirely without guidance" as to the scope of requirement, *Exxon Research and Eng'g Co. v. United States*, 265 F.3d 1371, 1379 (Fed.Cir.2001), adrift without the "objective anchor" which makes a term definite, *Datamize*, 417 F.3d at 1350. Where, as here, the term in question expresses a measure of degree, "the district court must determine whether the patent's specification provides some standard for measuring that degree." *Seattle Box Co. v. Indus. Crating & Packing, Inc.*, 731 F.2d 818, 826 (Fed. Cir.1984). For understandable reasons of fundamental fairness to others practicing the art, the presence or absence of a standard "cannot depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention." *Datamize*, 417 F.3d at 1350.

The terms "not interfering substantially" and "does not substantially interfere" appear in Claims 1, 42, and 48 of the '767 Patent; Claim 1 of the '824 Patent; and Claims 1 and 2 of the '928 Patent. In Claim 1 of the '824 patent, the term appears as follows: "said linkage group not interfering substantially with the characteristic ability of said compound to hybridize with said nucleic acid or of A to be detected." The Court's Claim Construction Ruling read this to mean that "the linkage group neither substantially interferes with the ability of the compound to hybridize with the nucleic acid nor substantially interferes with the ability of A to be detected." *Enzo Biochem*, 2006 U.S. Dist. LEXIS 74570 at 17.

Defendant contends that a person of skill in the art would not be able to determine from the specification how to measure "interference" in the context of "hybridization" and "detection."[7] Defendant also urges that the specification fails to provide guidance as to how to assess whether "interference" is present, since the significance of nucleotide alteration may vary according to the length of a polynucleotide (*i.e.*, the alteration of a single nucleotide would affect hybridization more profoundly on a shorter chain than on a longer one).

For its part, Enzo argues that this Court construed the term during the claim construction phase, and is therefore prevented from finding the term indefinite, citing two recent decisions from the Federal Circuit, *Energizer Holdings, Inc. v. Int'l Trade Comm'n*, 435 F.3d 1366, 1371 (Fed.Cir.2006) (noting that "[a] claim that is amenable to construction is not invalid on the ground of indefiniteness") and *Aero Prods. Int'l, Inc. v. Intex Recreation Corp.*, 466 F.3d 1000, 1016 (Fed.Cir.2006) (stating the corollary, that "if a claim is not amenable to construction, the claim is invalid as indefinite under 35 U.S.C. § 112, ¶ 2").

However, in both *Aero Products* and *Energizer*, the trial court had assigned precise definitions to the terms at issue during the claim construction phase.

---

[7] Plaintiffs emphasize that words of degree like "substantially" are not *per se* indefinite, *see, e.g., Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1575-76 (Fed.Cir.1986) ("so dimensioned"); *BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372-73 (Fed.Cir.2003) ("about"), but this contention misses the mark of Applera's argument, which is specific to whether the claims at issue sufficiently define the meaning of "not interfering substantially" and "does not substantially interfere."

In *Energizer*, the dispute centered on the phrase "said zinc anode," and the narrow question of whether the phrase properly referred to a specific antecedent term, 435 F.3d at 1368-1369. In *Aero Products*, the Federal Circuit weighed the definiteness of the phrase "complete hermetic seal," which the trial court had construed as meaning "a seal that does not require any additional parts to retain nearly or largely all of the air in the bed," 466 F.3d at 1008. The district court struck this compromise between two very specific construction proposals—the plaintiff's "seal that does not require any additional parts to retain 'nearly' or 'largely' all of the air in the bed such that the bed maintains its desired firmness for the expected duration of use," and the defendant's terser "nearly or largely impervious to air," *id.*

Here, the parties have presented this Court not with specificity, but with an adverbial phrase which, when added by the plaintiff as an amendment to the original patent in 1986,[8] was presumably meant to distinguish the Ward method of detection and hybridization from other methods which did cause substantial interference. At construction, neither party proposed a concrete definition for "substantial interference" expressed in signal-to-noise ratios, temperature, time, or any other laboratory metric which a practitioner could use as a milepost when performing hybridization and detection. Enzo proposed that the term be taken to mean, recursively, "not rendering impractical or overly difficult," Pl.'s Cl. Constr. Memo [Doc. # 89] at 23. Applera,

---

[8] Supplemental Amendment application dated Mar. 21, 1986 reproduced at defendant's memo in support of summary judgment on invalidity [Doc. # 185], Ex. 23.

meanwhile, proposed that the term be read as effectively meaning that the binding procedure function transparently, such that:

> that the ability of A (when attached to B via said linkage group) to form a detectable complex is essentially identical to the ability of A to form a detectable complex when directly attached to B.

Def.'s Cl. Constr. Memo [Doc. # 91-2] at 22-23. Beyond that, the parties' arguments on both construction and definiteness of the key phrase has been comparatively sparse, with defendants reserving argument on construction of "substantial interference" in the interest of arguing for indefiniteness at summary judgment,[9] and plaintiffs' reply construction brief not even listing "substantial interference" as an area of dispute.[10] Faced with the parties' two alternative meanings of "substantial interference," this Court chose to use the term to limn the behavior of the linkage group, but could not affix a more precise technical definition.[11]

Defendant's expert Kricka states in his report that "[t]he term 'not interfering substantially' in the context of 'hybridization' and/or 'detection' does not appear anywhere in the specification outside of the claims," and thus "provides no guidance to allow one skilled in the art to measure 'interference' in the

---

[9] Defs.' Cl. Constr. Br. at 22.

[10] *See* Pl. Reply Cl. Constr. Br. [Doc. # 98] at i.

[11] The Court ruled that "substantial interference" will be taken as meaning that "the linkage group neither substantially interferes with the ability of the compound to hybridize with the nucleic acid nor substantially interferes with the ability of [the A moiety] to be detected. *Enzo Biochem, Inc. v. Applera, Inc.*, 2006 U.S. Dist. LEXIS 74570 at 16.

context of 'hybridization' and 'detection.'" (Kricka Decl. ¶ 129.) Kricka further states that "there is no guidance in the specification for one to determine how to assess if there was any 'interference'" at all, given that "[w]hile a very minor alteration of a single nucleotide in a chain of three nucleotides would have a profound effect on the ability of that oligonucleotide to hybridize, the same modification on a longer oligonucleotide, such as one having 50 or 100 nucleotides, might not have any effect on hybridization." (*Id.* ¶ 130.) Defendant notes that Enzo's Vice President Dr. Dean Engelhardt testified that he did not know how one should measure the attribute of not substantially interfering. (Jan. 16, 2007 Engelhardt Dep., Def. Ex 25, at 128-29.) Similarly, Enzo's Vice President of Clinical Affairs, Dr. Barbara Thalenfeld, when asked how she would "measure whether only the linkage group does or does not interfere with hybridization" or "if the linkage group itself was interfering with the ability of the reporter to be detected," responded "I don't know." (Thalenfeld Dep., Def. Reply Ex. 6, at 178-79.)

The plaintiffs, relying upon the opinion of expert Sinden, argue that the term is sufficiently definite. Sinden opined that "substantial interference" is "clear and plain language" which denotes the point at which [something] will "prevent you from getting the experiment to work." (Apr. 13, 2006 Sinden Dep., Pls. Opp. Ex. 11, at 138:11-15). Sinden's report observes that the term means that "the linkage group may interfere with hybridization and detection so long as the interference is not substantial, *i.e.*, an amount that would render hybridization or detection impractical or overly difficult." (Sinden Report, Pls. Ex. 17, at 29). He also explained at his deposition how

temperature affects DNA hybridization and that a linker arm that altered the melting temperature of particular DNA would bear on "substantial interference." (Apr. 13, 2006 Sinden Dep., Pls. Opp. Ex. 11, at 134-36.)[12]

While arguing that the approach of the point of failure ("impractical or overly difficult"), is measurable in terms of "degrees of interference" (Apr. 13, 2006 Sinden Dep., Pls. Opp. Ex. 11, at 139:2-3), when pressed to identify the precise point at which interference ripens to substantiality, Sinden stated:

> It's probably in the hands of the experimenter. Clearly, if it didn't work at all, it wouldn't work. If it worked 50 percent and you were able to get your signal and publish a paper, you may go with it.

(*Id.* at 139:8-12.) Moreover, Sinden concedes that inasmuch as his report equates substantial interference with the point at which hybridization or detection becomes overly difficult, "[o]verly difficult may mean different things to different people." (Apr. 13, 2006 Sinden Dep., Def. Ex. 9, at 139-40.) Sinden's testimony would thus seem to corroborate Kricka's view that the face of the patent's specification provides no standalone gauge of "substantial interference," but rather requires experimentation in

---

[12] For his part, Kricka admits that "melting temperature of modified polynucleotides could conceivably be one measure of the effect of a linker arm on hybridization." (Kricka Decl. ¶ 129, citing Claim Construction Ruling at *16.) Even though Kricka and Sinden agree that melting temperature could have an effect on hybridization, plaintiffs have not pointed to anything in the patents instructing a person of skill in the art on how to determine substantiality of interference based upon melting temperature of polynucleotides.

order to determine where the claims set forth in the Patents become useful. Left to Sinden's interpretation, the Patent claims would cover any interactions which succeed, but not those which do not—rendering "substantial" a nullity. Moreover, it is instructive that neither Thalenfeld nor Engelhardt, both scientists and Enzo executives, could conjecture a means of determining substantiality of interference.

As this Court understands that allegations of indefiniteness may not be rebutted merely by the unrestrained, subjective opinion of the inventor, the claims must fail. In *Datamize*, the Federal Circuit affirmed a finding of indefiniteness where a patent specification purported to cover the creation of "aesthetically pleasing" elements in a computer graphical user interface. The deficiency in such a term, the Court found, was that Datamize had "offered no objective definition identifying a standard for determining when an interface screen is 'aesthetically pleasing,'" *Datamize*, 417 F.3d at 1342, but instead simply provided the testimony of an expert who listed elements of design which would lead one skilled in the art to deem a given user interface "aesthetically pleasing." The Court found that an expert's list of elements or indices alone "fails to explain how the parameters should be evaluated or weighed to reach the conclusion" that a given creation meets the patent's subjective standard. *Id.* at 1354, *see also Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1339 (Fed.Cir.2003) (affirming judgment of invalidity where the proper temperature at which a crucial step in the manufacturing-process invention was to take place was provided only by the testimony of patent holder's expert).

The Federal Circuit's treatment of indefiniteness in *Exxon* also informs this Court's decision. The two patents at issue in that case covered "improvements in what is known as the Fischer-Tropsch process for converting natural gas to liquid hydrocarbon products," *Exxon*, 265 F.3d at 1373, which, if implemented, would "increase[ ] the relative catalyst productivity in the Fischer-Tropsch reaction by at least 30%" and "optimally operat[e] a slurry bubble column . . . to produce hydrocarbon products at an increased rate." *Id.* at 1374. While the trial court had determined that four of Exxon's claims were indefinite for indefiniteness, the Federal Circuit reversed. Three of those claims centered on numerical terms,[13] but the analysis of most interest here is the Federal Circuit's treatment of a term which was not expressed within a mathematical formula, "substantial absence of slug flow."[14] In the district court, defendants had argued that gauging the substantiality of slug flow was not possible given that the specification did not set forth the proper means by which slug flow was to be measured. The Federal Circuit found the term to be sufficiently definite when read within the context of the entire patent, i.e. a system by which to increase efficiency of the Fischer-Topsch reaction by at least

---

[13] *See Exxon Research and Eng'g*, 265 F.3d at 1377 (deeming "to increase substantially" sufficiently definite where patent specification defines such an increase in catalyst activity as being between between 30-75%), *id.* at 1378 (holding "for a period sufficient" to be definite where the patent specification set out a minimum time period for sufficiency, but not a maximum time), *id.* at 1382 (finding that specification that particles be of an "average diameter" set forth in a mathematical formula acceptably definite).

[14] Apparently referring to the movement of large gas bubbles through the reactor.

30%. Because the patent specification taught that slug flow interferes with the efficient completion of the patented method, the Court held that the substantial absence of slug flow "can be determined with reference to whether reactor efficiency is materially affected," as measured by identifiable data points such as mass transfer performance. *Exxon*, 265 F.3d 1380-1381. Thus, by measuring the efficiency of their reactions—the innovation claimed by Exxon—practitioners could determine whether or not a particular procedure infringed upon Exxon's patent.

By contrast, the Ward patents do not set forth improvements upon a known process, but rather, describe a new procedure of non-radioactive detection and hybridization which does not cause "substantial interference" with a successful result. The specifications neither set forth how one would gauge substantial interference, nor delimit the threshold at which interference with the procedure prevents Ward's method from being implemented. As plaintiff's expert Sinden frankly admitted, substantial interference has thus been left to the experimenter to determine the conditions under which detection and hybridization either succeeds or fails. Although the patent expresses a term of degree ("substantial interference"), expert testimony has shown the term to be an illusory yardstick which, if permitted to stand, would sweep all successful hybridization and detection into the ambit of the patents' coverage, while excluding any unsuccessful procedures. This effect would be entirely unlike Exxon's patents, which covered only those Fischer-Tropsch reactions which were made observably more efficient by use of the patented methods. It cannot be the case that a term added as a limiting clarification to the Ward

patents can now be used to amplify the patents' coverage.

In sum, plaintiff has been caught in one of patent law's traps: having used language in its patent application which stakes out the zone of exclusivity for its invention, the plaintiff must now be able to show that its language is nonetheless definite enough to put others skilled in the art on notice of what has been patented. Because defendant has proven by clear and convincing evidence that the term "interfering substantially" in Claim 1 of the '824 Patent; Claims 1, 42, and 48 of the '767 Patent; and Claims 1 and 2 of the '928 Patent is indefinite, summary judgment of invalidity for indefiniteness is granted on these patent claims.

D. *Anticipation*

Although the indefiniteness of the claims at issue is fatal, thoroughness counsels addressing all of the parties' remaining arguments. As a third ground of invalidity, defendant asserts that the '824, '767, and '928 patents were anticipated by three prior art references published before April 17, 1981 (the date that the original Ward patent application was filed): a journal article by Alfred Pingoud, *et al.* published in 1977; a journal article by Hiroshi Kasai, *et al.* published in 1979; and a doctoral thesis by J.G.J. Bauman published in 1980. (*See* Alfred Pingoud, *et al.*, "Fluoresceinylthiocarbamyl-tRNA: a useful Derivative of tRNA (E.coli) for Physiochemical Studies," *Nucleic Acids Res.* (1977) ("Pingoud"), Def. Ex. 27; Hiroshi Kasai, *et al.*, "Specific Fluorescent Labeling of 7-(aminomethyl)-7-deazaguanosine Located in the Anticodon of tRNA Isolated from E. Coli Mutant," *Nucleic Acids Res.* (1979) ("Kasai"), Def. Ex. 28;

J.G.J. Bauman, "Cytochemical Detection of Specific Nucleic Acid Sequences Development and Application of In Situ Hybridisation Methods for Fluorescence Microscopy" (doctoral dissertation) (1980) ("Bauman"), Def. Ex. 29.) Specifically, Applera contends that Kasai anticipates the '767 and '824 Patents; Pingoud anticipates the '767 and '928 Patents; and Bauman anticipates all three patents. Plaintiffs argue that none of the three publications discloses every claim asserted as construed by the Court and that a genuine issue of material fact exists as to whether the articles are enabling references that qualify as "prior art."[15]

---

[15] The Court disposes briefly of Sherman's general attack on the three references for failing to meet "the standard that an organic chemist in the early 1980's would have used in order to determine whether or not a new organic molecule had been synthesized" and as thus being non-enabling (Sherman Decl. ¶ 33). Without citation to any authority, Sherman conclusorily states that a publication "lacking a sufficient number of [10] criteria" would not be considered to provide necessary disclosure to enable one of skill in the art to make and use a new chemical substance, and thus that Kasai and Pingoud in particular should be rejected as prior-art references because they are not enabling. (*Id.*) Sherman's proffered rubric, however, is unsubstantiated and thus rejected as a general argument against defendant's anticipation claims. Moreover, as defendant points out, Kasai and Pingoud were in any case published in the journal Nucleic Acids Research; and for a reference to be enabling, "all that need be shown is that one of skill in the art could make the disclosed compounds," not that it was actually made. (Def. Reply Mem. at 7-8, citing *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir.1985) ("[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. . . . It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.").) *See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d

Whether a patent claim is anticipated under 35 U.S.C. § 102 is a question of fact requiring element-by-element evaluation of the disclosure of the claims in the prior art reference, as "each and every limitation . . . either expressly or inherently" must be disclosed, *Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc.*, 246 F.3d 1368, 1374 (Fed.Cir.2001). "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Elan Pharms., Inc.*, 346 F.3d at 1054 (internal quotation marks and citation omitted).

1. *Kasai*

Kasai "describes a procedure for fluorescent labeling of E. coli preQ1-containing $tRNA^{Tyr}$ with dansyl chloride." (Kasai, Def. Ex. 28, at 232.) The article reports that "[t]he modified $tRNA^{Tyr}$ was found to be active both in amino-acylation and in binding to ribosomes" and that "this fluorescent probe should be useful for conformational studies on tRNA." (*Id.*) Defendant argues that Kasai discloses a labeled polynucleotide sequence (dansyl-tRNA) that meets each limitation of the relevant claims of the '767 and '824 Patents.

a. *'767 Patent*

To illustrate what it alleges to be the anticipation of the '767 patent, Applera focuses on the sugar moiety-containing oligo-/polynucleotide of Claim 48, arguing that Kasai's tRNA compound includes

---

1368 (affirming partial denial of summary judgment of invalidity for anticipation where anticipatory experiment "enabled the performance of [antitumor drug administration] steps even though [it] did not achieve a favorable outcome").

-CH2-NH-, the aminomethyl linkage group whose structure is "preferred" in the Ward Patents specification, which constitutes Claim 8 of the '767 Patent and Claim 16 of the '928 Patent. Defendant claims that Kasai's tRNA compound hybridizes with complementary polynucleotides and becomes detectable via measurement of the fluorescence of the dansyl moiety, Kasai Fig. 2, Def. Ex. 28, at 235—thus, because hybridization and detection are made possible in this fashion, that Kasai meets the "not substantially interfere" limitation. Although this Court has determined that the "substantially interfere" language in the Ward Patents is the basis for their invalidity, interpretation of the phrase for purposes of anticipation does not affect the invalidity ruling.

Enzo's expert Sherman disputes the satisfaction of the "not substantially interfere" limitation by stating that the aminomethyl group serving as a linker arm in the compound "would not provide sufficient rigidity to prevent significant interference with hybridization of a complementary polynucleotide. Indeed, one would predict based on the flexibility of this functional group and the concomitant high degree of motion, there would be significant interference due to free rotation about the single bonds." (Sherman Decl. ¶ 44.) However, as defendant notes, Sherman offers no support, experimental, literary, or otherwise, for this assertion. In addition, implicit in Sherman's observation about the aminomethyl-group linker is a definition of substantial or significant interference as allowing for hybridization, which conflicts with Sinden's interpretation of the term "not substantially interfere" as "it can't prevent you from getting the experiment to work." See Apr. 13, 2006 Sinden Dep., Def. Ex. 9, at 138.

A general retort made by plaintiffs is that Kasai cannot be anticipatory because it is directed to naturally substituted bases, *viz.* preQ1, which Enzo contends is "specifically excluded from the Ward Patent claims." (Sherman Decl. ¶ 42.) Enzo cites the specification, which reads that "7-deazapurines useful in this invention must not be naturally substituted at the 5- or 7-positions, respectively." ('824 Patent at 7:64-67.) Defendant responds that Sherman relies on the specification rather than the patent claims, impermissibly importing limitations into the claims for purposes of avoiding prior art. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed.Cir.2005). Moreover, Applera claims that the phrase from the specification is quoted out of context and in fact "refers to the fact that the Ward patents' described methods for adding linkage groups to the 5-position of pyrimidines and the 7-position of 7-deazapurines will not work if there is already a carbon-carbon bonded substituent at these positions such as in thymine, 5-methylcytosine, and 5-hydroxymethylcytosine," *i.e.*, that "modified bases derived from bases lacking natural substitutions at the 5- or 7-positions 'are more readily prepared or used or both, and therefore are presently preferred.'" (Kricka Reply Decl. ¶ 8, citing '824 Patent at 7:53-57.) Kricka opines that "Kasai discloses how to synthesize 7-(aminomethyl)-7-deazaguanosine and react this compound with dansyl chloride. . . . Therefore, one of skill in the art could make an 'unnaturally' substituted 7-deazapurine and label it with a fluorescent dye if they wished." (*Id.* ¶ 11.) The Court agrees that the Ward Patent claims do not contain a specific limitation which excludes all naturally-occurring linkage groups (modified 7-deazapurine bases), and

thus, a finding that Kasai anticipates the '767 Patent is not precluded. Defendant has met its burden of proving Kasai's anticipation of each limitation of every asserted claim of the '767 Patent.

b. *'824 Patent*

The arguments with respect to Kasai's alleged anticipation of the '824 Patent, including the non-naturally occurring argument, are basically identical to those above for the '767 Patent. The '824-specific arguments are addressed here.

Kasai discloses that "binding of danyslated Tyr-tRNA$^{Tyr}_{preQ1}$ to E. coli ribosomes was stimulated by template, poly(U, A, C)." (Kasai, Def. Ex. 28, at 236.) According to Kricka this anticipates Claim 1's method for detecting nucleic acids (poly(U, A, C) or poly(U, C) containing ribosomal RNA) that hybridize or bind with the dansyl-labeled polynucleotide tRNA^{Tyr}. (Kricka Decl. ¶ 68-76; Kasai, Def. Ex. 28, at 236-38.) Sherman disputes this by asserting that the tRNA in Kasai is used for "conformational characterization," not detection of nucleic acids, and does not disclose hybridization between two complementary polynucleotides, but between a polynucleotide and a stimulated ribosome. (Sherman Decl. ¶¶ 51-53.) However, Kricka explains that the ribosomal RNA of E. coli used in Kasai is referenced as a type of polynucleotide in the '824 Patent ('824 Patent at 17:24), and thus that when the "tRNA binds to a ribosome, portions of the tRNA hybridize to portions of the ribosomal RNA at various stages in the translation process. At the same time, the anticodon portion of the tRNA hybridizes with codon portions of another polynucleotide" (Kricka Reply Decl. ¶ 29). Indeed, Kasai notes that "[b]inding of [^{14}C]Tyr-tRNA to E. coli ribosomes in the presence of polynucleotide

template was carried out as reported by Nishimura *et al.*" (Kasai, Def. Ex. 28, at 233), indicating that tRNA-ribosome bonding was an established form of polynucleotide hybridization. As plaintiffs fail to rebut defendant's proof of anticipation, and for the reasons stated above with respect to the '767 Patent, the Court finds that defendant has proven by clear and convincing evidence that Kasai anticipates every claim of the '824 Patent.

2. *Pingoud*

Pingoud describes the labeling at "uncommon base Q"—which had recently been identified when Pingoud was published and was later supplanted in Kasai by the preQ1 nucleoside—of the modified tRNA polynucleotide "FTC-$tRNA^{Tyr}$," and shows to what extent the modification affects the biological activity of the tRNA. (Pingoud, Def.Ex.27.) Applera contends that Pingoud is an anticipatory reference as to the '767 and '928 Patents.

a. *'767 Patent*

Defendant contends that Pingoud discloses the labeled polynucleotide FTC-$(QU)_n$, whose structure is described in the claims of the '767 patent. The structural identity of the nucleotides is substantially undisputed, except that plaintiffs again make the same argument as with Kasai that apropos the linkage group, the "does not substantially interfere" limitation is unmet, and that the "naturally substituted" limitation is implicit in the claim—the same arguments made with respect to anticipation based on Kasai. For the same reasons these arguments were rejected *supra*, the Court rejects them here, and the Court has in any case concluded that Patent '767 is invalid for anticipation by Kasai.

b. *'928 Patent*

Kricka opines that Claims 1 and 2 of the '928 patent were disclosed by Pingoud. As to Claim 1, Applera reads Pingoud as disclosing a fluorescein labeled 7-deazaguanosine nucleoside that is "[a] compound useful as a probe for detecting the presence or absence of a nucleic acid" to either detect the presence of $tRNA^{Tyr}$ when the nucleoside is incorporated into the polynucleotide, or by digesting the polynucleotides to individual nucleosides and then detecting the disclosed labeled nucleoside. As to Claim 2, defendant makes the same arguments for the terms of that claim which are identical to that of Claim 1 and adds that the labeled polynucleotide $FTC\text{-}(QU)_p$ is useful as a probe to detect $tRNA^{Tyr}$.

The locus of debate with respect to the '928 Patent concerns the "A" moiety in Claims 1 and 2, which "represents at least three carbon and an indicator molecule," and intersects with the question of whether both indirect and direct detection are disclosed by the Patent. As the Court determined *supra* that Applera has failed to meet its burden of proving invalidity for lack of written description as to direct detection, the Court evaluates whether Pingoud is anticipatory as to both indirect and direct detection. The parties agree that in order to have anticipated the '928 Patent, Pingoud's "A" moiety must consist of a fluorescein dye indicator molecule and another portion containing at least three carbon atoms. Defendant argues that "the fluoresceinyl-thiocarbamyl moiety [in Pingoud] is split into two components: a portion of the fluorescein dye that can independently act as a fluorescent dye and another portion containing at least three carbons." (Def. Mem. at 39.) Enzo contests that the moiety can really be

"split," and points to Kricka's testimony "that one of skill in the art would not consider breaking up fluorescent molecules into their constituents." (Kricka Reply Decl. ¶ 33; Kricka Decl. in Supp. of Def. Mot. for Summ. J. of Non-Infr., Pls. Ex. 25 ¶¶ 30, 31.) Although Kricka defends his comment as responsive to Sinden's "advocat [ing] breaking single fluorescent dyes into constituent parts" (*id.*), Sinden's testimony was directed to splitting a compound consisting of a fluorescein donor dye attached to a rhodamine acceptor dye, *i.e.*, the structure of defendant's allegedly infringing compounds. (Sinden Decl. in Supp. of Pls.' Opp. to Def. Mot. of Summ. J. of Non-Infr., Pls. Ex. 24, ¶¶ 29-31.)

As the party claiming invalidity, defendant's burden is high: Applera must prove invalidity by "clear and convincing evidence as to underlying facts," *Rockwell Int'l Corp.*, 147 F.3d at 1364. Here, the combination of Kricka's disavowal that one would split fluorescent dyes like that in the Pingoud moiety, taken together with defendant's failure to show that Sinden's discussion of splitting applied outside the context of Applera's fluorescein-rhodamine compound, prevents this Court from concluding that Pingoud's moiety meets the three-carbon-plus-indicator-molecule limitation in the '928 Patent, and thus defendant's Motion of invalidity for anticipation based on Pingoud is denied with respect to '928 Patent Claims 1 and 2.

3. *Bauman*

The third article claimed to be prior art is a doctoral thesis written by Dutch scientist J.G.J. Bauman, which was publicly available more than one year

prior to the filing of the original Ward patent.[16] Chapter 8 of Bauman's thesis sets forth a method of indirect detection involving the incorporation of pyrimidine nucleotides labeled with a Hg-Glutathione-Trinitrophenyl ("TNP") hapten and fluorescent antibodies to TNP. Defendant claims that Bauman shows that the hapten-labeled polynucleotide can be used as a probe in a hybridization assay to detect the presence of nucleic acids in a sample, and is thus an anticipatory reference of the three Ward Patents.[17]

The parties make generalized arguments not specific to the particular claims. First, the parties dispute whether the mercury-glutathione linker (the mercury bonds are the C-Hg bond between A and B and the Hg-S bonds in A) in Bauman is usable for typical hybridization experiments. Bauman explains that under certain conditions there were "[p]roblems observed in hybridising mercurated polynucleotides." (Bauman, Def. Ex. 29, at 161.) However, it notes that "[t]he loss of mercury during the hybridisation as a result of the thermal instability of the -C-Hg-bond (Dale and Ward, 1975) can be avoided by using low tempoeratures and formamide containing buffers." (*Id.* at 162.) According to Applera, this remedial prescription makes the Bauman compound usable in hybridization, and plaintiffs offer no evidence to

---

[16] Enzo's concern about the non-disclosure of the full Bauman reference was cured by submission of the entire dissertation and accompanying documents with Applera's reply memorandum.

[17] Sherman argues that Claim 21 of the '824 Patent and Claim 70 of the '767 Patent should not be deemed asserted as anticipated by Bauman because they are not specifically addressed in Kricka's chart illustrating the anticipation claimed. (Sherman Decl. ¶¶ 66, 67.) However, these claims are in fact addressed in that chart. (*See* Kricka Decl.App. A. at 18, 32.)

rebut this, except to cite one sentence of the Ward Patents specification,[18] Sherman Decl. ¶ 72. However, this section of the specification does not address mercury, and Sherman does not explain how this bears on the analysis. Thus, the inaptness of mercuriated polynucleotides for hybridization does not dispose of the anticipation argument.

Second, Enzo and Applera disagree as to whether the mercury ligand in Bauman substantially interferes with hybridization. The indirect detection method in Bauman begins with RNA "mercurated by incubation in mercuric acetate," but at the next step, "[t]he acetate ligand of the mercuri-nucleotides is replaced by the CN ion, in order to facilitate hybridisation." (Bauman, Def. Ex. 29, at 142-43.) That this alteration is required, plaintiffs argue, signifies that "the glutathione linkage group interferes with hybridization" (Sherman Decl. ¶ 74). Moreover, Enzo points out that Bauman uses the synthetic homopolymer poly(U) in its experiments, which plaintiffs claim "provides an increased incidence of hybridization allowing for a greater amount of interference to occur without resulting in failure of hybridization," Sherman Decl. ¶ 76. However, in addition to Sherman's failure to support his statement that use of Poly(U) results in increased hybridization and thus greater interference, Applera correctly points out that the Ward Patents do not preclude use of unnatural homopolymers; in fact, the specification itself states, "Another embodiment of

[18] '824 Patent at 6:64-68 reads: "[T]he physical and biochemical properties of polynucleotides containing small numbers of probe substituents should not be significantly altered so that current procedures using radioactive hybridization probes need not be extensively modified."

this invention involves detection of poly A-containing sequences using poly U" ('824 Patent at 24: 51-54). Thus, the Bauman references satisfy the "not substantially interfering" limitation in the Ward Patents.

The third aspect bearing on whether Bauman is anticipatory stems from the Court's construction of the Ward Patents as disclosing both direct and indirect detection. The claim language "wherein the moiety A comprises an indicator molecule" and "wherein A comprises an indicator molecule" from the '767 and '824 Patents, was interpreted in the Court's Claim Construction Ruling interpreted to mean "that A may be a part of or the entire signaling moiety." *Enzo*, 2006 U.S. Dist. LEXIS at 11-12. In no uncertain terms, the Court concluded at claim construction that "the plain language and structure of the '824 and '767 Patents indicate that these patents cover both direct and indirect detection." *Id.* at 9. While the parties agree that Bauman does not address direct detection, Applera argues that it need not include both direct and indirect detection to be anticipatory. However, the caselaw is clear that in order for a reference to be anticipatory, it must "disclose every limitation of the claimed invention, either explicitly or inherently," *Liebel-Flarsheim Co.*, 481 F.3d at 1381, and as Bauman only discloses indirect detection, it is not an anticipatory reference rendering Patents '767 and '824 invalid. Summary judgment of invalidity for anticipation is thus denied based on Bauman as regards the '767 and '824 Patents.

Lastly, with respect to the '928 Patent, in addition to the earlier discussion of whether B meets the "not substantially interfering" limitation, plaintiffs' expert Sherman applies the same reasoning discussed above

with respect to non-disclosure of direct detection to argue against anticipation. However, as diagrammed in defense expert Kricka's comparative chart, the three-carbon-plus-indicator-molecule structure is supported by the compound set out in Bauman: the complex consisting of the Hg-Glutathione-TNP, the rabbit TNP-antibody, and the swine antibody to the rabbit antibody. Kricka Decl.App. A at 83-84. As the other limitations are also diagrammed and well supported by defendant's expert, plaintiffs' brief retort is insufficient to rebut the evidence presented that '928 Patent Claims 1 and 2 are anticipated by Bauman. Summary judgment is granted on grounds of anticipation with respect to the '928 Patent.

III. *Conclusion*

Accordingly, the Court concludes that the Claims 1, 2, 8, 11, 13, 42, 46, 47, 48, 49, 50, 51, 67, 68, 70 of the '767 Patent; Claims 1, 18, 19, 21, 26, 28, 32, 33 of the '824 Patent; and Claims 1 and 2 of the '928 Patent are invalid based on anticipation by prior art. Defendant Applera's Motion for Summary Judgment of Invalidity [Doc. # 181] is therefore granted. The Clerk is directed to close this case.

IT IS SO ORDERED.

APPENDIX C

UNITED STATES COURT OF APPEALS
FEDERAL CIRCUIT

No. 2009-1281

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., AND YALE UNIVERSITY,
Plaintiffs-Appellants,

v.

APPLERA CORP. AND TROPIX, INC.,
Defendants-Appellees.

May 26, 2010

Before MICHEL, *Chief Judge*, NEWMAN, MAYER, PLAGER,* LOURIE, RADER, BRYSON, GAJARSA, LINN, DYK, PROST, and MOORE, *Circuit Judges*.

PLAGER, *Circuit Judge*, dissents from the denial of the petition for panel rehearing.

ORDER

PER CURIAM.

Defendants-Appellees Applera Corp. and Tropix, Inc. filed a combined petition for panel rehearing and rehearing en banc. The panel requested a response from Plaintiffs-Appellants Enzo Biochem, Inc., Enzo Life Sciences, Inc., and Yale University. The court

---

* Judge Plager participated only in the decision on the petition for panel rehearing.

granted Defendants-Appellees leave to file a reply. The petition for rehearing was considered by the panel that heard the appeal, and thereafter the petition for rehearing en banc, the response to the petition, and reply were referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The petition of Defendants-Appellees for panel rehearing is denied.

(2) The petition of Defendants-Appellees for rehearing en banc is denied.

(3) The mandate of the court will issue on June 2, 2010.

ON PETITION FOR PANEL REHEARING

PLAGER, *Circuit Judge*, dissenting from the denial of the petition for panel rehearing.

I respectfully dissent from the denial of the petition for panel rehearing on the question of indefiniteness. Despite the varying formulations that this court has used over the years in describing its "indefiniteness" jurisprudence to which the petitioner in this case points, the general conclusion from our law seems to be this: if a person of ordinary skill in the art can come up with a plausible meaning for a disputed claim term in a patent, that term, and therefore the claim, is not indefinite.[1] At least not so indefinite as

---

[1] *See, e.g., Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed.Cir.2005) ("Only claims 'not amenable to construction' or 'insolubly ambiguous' are indefinite." (citing *Novo Indus., L.P. v. Micro Molds Corp.*, 350 F.3d 1348, 1353 (Fed. Cir.2003); *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d

to run afoul of the statutory requirement that claims shall "particularly point[ ] out and distinctly claim[ ] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, second paragraph.

The corollary derived from this understanding is that if several persons of ordinary skill come up with competing but plausible interpretations of a disputed term—as is typically the case with competing "expert witnesses" in patent infringement litigation—the problem is not one of an inherently ambiguous and potentially indefinite claim term, but rather the problem becomes simply one of picking the "right" interpretation for that term.[2] Since picking the "right" interpretation—claim construction—is a matter of law over which this court rules, and since the view of the trial judge hearing the case is given little weight, so that the trial judge's view on appeal becomes just a part of the cacophony before this court, it is not until three court of appeals judges randomly selected for that purpose pick the "right" interpretation that the public, not to mention the patentee and its competitors, know what the patent

---

1332, 1338 (Fed.Cir.2003); *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed.Cir.2001))).

[2] Broad, to the point of inherently ambiguous, claim drafting is not just a matter of poor drafting skills on the part of some lawyers who prosecute patent applications. On the contrary, the art of broad claim drafting is a prized talent—clients are openly urged to use "broad patent protection both offensively to block competitors from the marketplace, and defensively to serve as a bargaining chip against potential patent infringement suits" and to "file patents to cover all aspects of the core technology . . . to create a 'picket fence' of protection." David J. Dykeman and Joanna T. Brougher, *File, Protect, Update, Defend*, Corporate Counsel, May 1, 2010, http://www.law.com/jsp/cc/PubArticleCC.jsp?id=1202447671049.

actually claims. The inefficiencies of this system, and its potential inequities, are well known in the trade.

The United States Patent and Trademark Office ("PTO"), by contrast, appears to be taking steps to give the statutory requirement real meaning. In 2008, the patent examining corps was given a five-page instruction on "Indefiniteness rejections under 35 U.S.C. § 112, second paragraph."[3] The memo initially observes that "[t]he primary purpose of the definiteness requirement for claim language is to ensure that the scope of the claims is clear so that the public is informed of the boundaries of what constitutes infringement of the patent."[4] The memo reviews in detail a recent opinion of this court, following which the memo states the position of the PTO: "If the language of a claim, considered as a whole in light of the specification and given its broadest reasonable interpretation, is such that a person of ordinary skill in the relevant art would read it with more than one reasonable interpretation then a rejection of the claim under 35 U.S.C. § 112, second paragraph, is appropriate."[5]

This memo was followed later in the year by a rare precedential opinion issued by the Board of Patent Appeals and Interferences ("Board") in *Ex parte Miyazaki*.[6] The Board noted that this court has in

---

[3] Memorandum from John Love, Deputy Commissioner for Patent Examination Policy, to Technology Center Directors and Patent Examining Corps (Sept. 2, 2008), *available at* http://www.uspto.gov/web/patents/memoranda.htm.

[4] *Id.* at 1.

[5] *Id.* at 2.

[6] No. 2007-3300, 2008 WL 5105055 (Bd. Pat.App. & Inter., Nov. 19, 2008).

post-issuance patent infringement cases held "that the definiteness requirement 'does not compel absolute clarity' and '[o]nly claims "not amenable to construction" or "insolubly ambiguous" are indefinite.'"[7] Recognizing that this court has never set forth a different standard of review for indefiniteness under 35 U.S.C. § 112, second paragraph, for pre-issuance pending claims as compared with post-issuance patent claims,[8] the Board concluded that the Federal Circuit's reading of the indefiniteness requirement was counter to the PTO's broader standard for claim construction during prosecution.[9] Accordingly, the Board announced that, "rather than requiring that the claims are insolubly ambiguous, we hold that if a claim is amenable to two or more plausible claim constructions, the USPTO is justified in requiring the applicant to more precisely define the metes and bounds of the claimed invention by holding the claim unpatentable under 35 U.S.C. § 112, second paragraph, as indefinite."[10]

The Board is clearly right in recognizing that the circumstances are different between pre-issuance and post-issuance application of the definiteness standard with regard to claim terms. At the same time, the PTO and the Board are clearly right in insisting that, if the public notice function of the patent law is to be honored, claim terms must particularly point out and distinctly claim the subject matter of the invention. In my view, this court's definiteness doctrine could go considerably further in promoting that objective than

---

[7] *Id.* at *4 (quoting *Datamize*, 417 F.3d at 1347).

[8] *Id.* at *6.

[9] *Id.* at *5.

[10] *Id.*

it currently does, with the not inconsequential benefit of shifting the focus from litigation over claim construction to clarity in claim drafting.

To begin the discussion of how this court could move in that direction, I would grant the petition for panel rehearing. The court now spends a substantial amount of judicial resources trying to make sense of unclear, overbroad, and sometimes incoherent claim terms. It is time for us to move beyond sticking our fingers in the neverending leaks in the dike that supposedly defines and figuratively surrounds a claimed invention. Instead, we might spend some time figuring out how to support the PTO in requiring that the walls surrounding the claimed invention be made of something other than quicksand.

I respectfully dissent from the loss of that opportunity through the panel's denial of rehearing.

APPENDIX D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF CONNECTICUT

[Filed Aug. 18, 2005]

No. 3:04-CV-929 (JBA)

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., and YALE UNIVERSITY,
Plaintiffs,

v.

APPLERA CORPORATION and TROPIX, INC.,
Defendants.

EXPERT REPORT OF LARRY J. KRICKA, D.Phil

* * * *

21. The ability of two complementary nucleic acid strands to hybridize can be used to perform a variety of tests. For instance, in hybridization assays, described in more detail in Section IV.D., a scientist will select or synthesize a nucleic acid with a known sequence of nucleotides, called a *probe*, specifically because the probe will hybridize with a complementary sequence of nucleotides in a target nucleic acid. This target nucleic acid, called an *analyte* or *target*, is usually a nucleic acid in a biological sample that the scientist wishes to detect the existence of, and possibly measure the amount of, in the sample. The probe will bind strongly and preferentially to complementary sequences in the analyte under hybridizable conditions creating a hybrid. After separating unhybridized probes or analyte from the hybrids by washing, the hybrids can be detected through use of a

label attached to or incorporated into the probe or the analyte. A label is a compound or an atom that has properties that make it either directly or indirectly detectable. (*See* Section IV.B. below on direct and indirect labeling.) Figure 6, shows an example of a basic hybridization assay where (1) nucleic acids from a sample are immobilized on a surface, (2) labelled probe is added, (3) unhybridized probe is washed away, and (4) the hybrids of labelled probe and analyte are detected by detecting the probe's label.

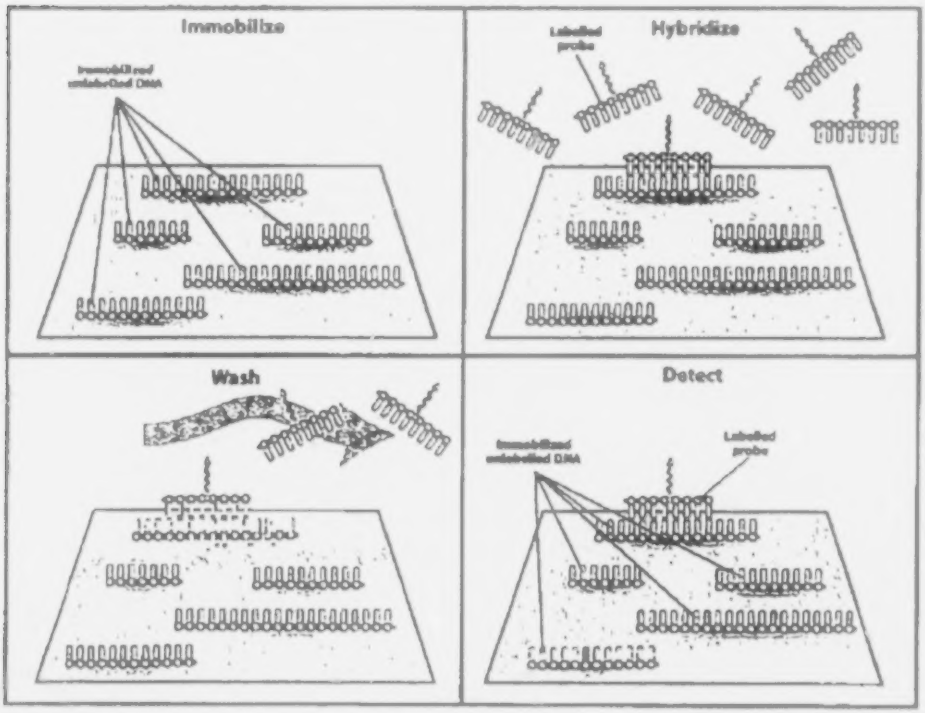


Figure 6

* * * *

Supreme Court, U.S.
FILED
NOV 1 1 2010
OFFICE OF THE CLERK

No. 10-426

IN THE

Supreme Court of the United States

APPLERA CORP. AND TROPIX, INC.,
Petitioners,

v.

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., AND YALE UNIVERSITY,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF IN OPPOSITION

JEFFREY A. LAMKEN
MARTIN V. TOTARO
MOLOLAMKEN LLP
The Watergate, Suite 660
600 New Hampshire Ave., NW
Washington, D.C. 20037
(202) 556-2000

MICHAEL HAWES
Counsel of Record
L. GENE SPEARS
AARON STREETT
BAKER BOTTS LLP
One Shell Plaza
910 Louisiana Street
Houston, Texas 77002-4995
(713) 229-1750
michael.hawes@bakerbotts.com

Counsel for Respondents

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D.C. 20002

QUESTION PRESENTED

Whether this Court should overrule *Eibel Process Co.* v. *Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923), and hold that 35 U.S.C. § 112's requirement of "claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention" precludes the use of relative terms like "substantially" and "approximately" in claims even though a person skilled in the art would understand, in light of the entire patent and existing knowledge, what is being claimed.

CORPORATE DISCLOSURE STATEMENT

Pursuant to Supreme Court Rule 29.6, respondents state at follows:

Enzo Biochem, Inc. is the parent of Enzo Life Sciences, Inc. Otherwise, there are no parents or corporations holding 10% or more of the stock of any of respondents.

TABLE OF CONTENTS

	Page
Question Presented	i
Corporate Disclosure Statement	ii
Preliminary Statement	1
Statement	4
I. Statutory Background	4
II. Proceedings Below	6
A. The Invention	6
B. The District Court's Decision	9
C. The Federal Circuit's Decision	10
Reasons For Denying The Petition	12
I. The Decision Below Does Not Conflict With Any Decision Of This Court Or Statutory Text	12
A. The Federal Circuit Correctly Applied This Court's Precedents Permitting Relative Terms Like "Substantially"	13
B. The Federal Circuit's Definiteness Standard Does Not Conflict With The Patent Statute	18
C. There Is No Conflict Between The Federal Circuit and The PTO	21
II. The Request For Further Review Falls Short of Justification	25
III. The Decision Below Is A Poor Vehicle	29
Conclusion	32

TABLE OF CONTENTS—Continued

Page

Appendix A – United States Patent No. 5,449,767 ..... 1a

Appendix B – Supplemental Amendment of March 21, 1986, U.S. Patent Application Serial No. 496,915 ..... 23a

Appendix C – Office Action of July 2, 1986, U.S. Patent Application Serial No. 496,915 ..... 36a

Appendix D – Amendment of December 31, 1986, U.S. Patent Application Serial No. 496,915 ..... 39a

Appendix E – Office Action of April 16, 1987, U.S. Patent Application Serial No. 496,915 ..... 45a

Appendix F – Letter of March 7, 1995 from Dr. Stephen Macevicz to Hon. Lawrence J. Goffney, Assistant Commissioner of Patents 50a

TABLE OF AUTHORITIES

Page(s)

CASES

Acacia Media Techs. Corp. v. *New Destiny Internet Group*, No. 05-CV-114, MDL Case No. 05-1665 (N.D. Cal. Oct. 23, 2009), *aff'd*, No. 2010-1081 (Fed. Cir. Oct. 7, 2010) 27

Amgen, Inc. v. *Chugai Pharm. Co., Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991) 24

Andrew Corp. v. *Gabriel Elecs., Inc.*, 847 F.2d 819 (Fed. Cir.), cert. denied, 488 U.S. 927 (1988) 15

Ariad Pharms., Inc. v. *Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc) 6

Atlantic Thermoplastics Co. v. *Faytex Corp.*, 970 F.2d 834 (Fed. Cir. 1992) 23

California v. *Rooney*, 483 U.S. 307 (1987) 25

CFMT, Inc. v. *YieldUP Int'l Corp.*, 349 F.3d 1333 (Fed. Cir. 2003) 6

Cutter v. *Wilkinson*, 544 U.S. 709 (2005) 30

Dann v. *Johnston*, 425 U.S. 219 (1976) 15

Deering Precision Instruments, LLC v. *Vector Distribution Sys., Inc.*, 347 F.3d 1314 (Fed. Cir. 2003), cert. denied, 540 U.S. 1184 (2004) 16

Demaco Corp. v. *F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387 (Fed. Cir. 1988) 23

Diamond v. *Diehr*, 450 U.S. 175 (1981) 14, 15

TABLE OF AUTHORITIES—Continued

Page

Dolbear v. *Am. Bell Tel. Co.*, 126 U.S. 1 (1888) 14

Eibel Process Co. v. *Minn. & Ontario Paper Co.*, 261 U.S. 45 (1923) ..... *passim*

Eli Lilly & Co. v. *Aradign Corp.*, 376 F.3d 1352 (Fed. Cir. 2004) 24

Enzo Biochem, Inc. v. *Applera Corp.*, No. 3:04cv929 (JBA), 2006 U.S. Dist. Lexis 74570 (D. Conn. Oct. 12, 2006) 9

Evans v. *Eaton*, 20 U.S. 356 (1822) 4, 5, 19

Ex Parte Miyazaki, 89 U.S.P.Q.2d 1207 (BPAI 2008) 22, 27

Exxon Research & Eng'g v. *United States*, 265 F.3d 1371 (Fed. Cir. 2001) 15

Festo Corp. v. *Shoketsu Kinzoku Kogy Kabushiki Co.*, 535 U.S. 722 (2002) 3, 16, 17

Fuller v. *Yentzer*, 94 U.S. 288 (1876) 21

Gen. Elec. Co. v. *Wabash Appliance Corp.*, 304 U.S. 364 (1938) 14, 17, 18, 19

Halliburton Energy Servs., Inc. v. *M-I LLC*, 514 F.3d 1244 (Fed. Cir. 2008) 16

Hamilton-Brown Shoe Co. v. *Wolf Bros. & Co.*, 240 U.S. 251 (1916) 3, 31

Hilton v. *S.C. Pub. Rys. Comm'n*, 502 U.S. 197 (1991) 2, 29

In re Katz, 687 F.2d 450 (C.C.P.A. 1982) 24

In re Marosi, 710 F.2d 799 (Fed. Cir. 1983) 11

In re Marzocchi, 439 F.2d 220 (C.C.P.A. 1971) 24

TABLE OF AUTHORITIES—Continued

Page

In re Morris, 127 F.3d 1048 (Fed. Cir. 1997) 22, 23

In re Zletz, 893 F.2d 319 (Fed. Cir. 1989) 22, 23

Kewanee Oil Co. v. *Bicron Corp.*, 416 U.S. 470 (1974) 31

Markman v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996) ..... *passim*

Merrill v. *Yeomans*, 94 U.S. 568 (1876) 2, 5, 20

Minerals Separation v. *Hyde*, 242 U.S. 261 (1916) 1, 13

Ortho-McNeil Pharm., Inc. v. *Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321 (Fed. Cir. 2007) 16

Payne v. *Tennessee*, 501 U.S. 808 (1991) 2

Permutit Co. v. *Graver Corp.*, 284 U.S. 52 (1931) 15, 18, 21

Praxair, Inc. v. *ATMI, Inc.*, 543 F.3d 1306 (Fed. Cir. 2008) 6

Quantum Corp. v. *Rodime, PLC*, 65 F.3d 1577 (Fed. Cir. 1995), cert. denied, 517 U.S. 1167 (1996) 15, 27

Sanofi-Synthelabo v. *Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008) 23

Smith v. *Snow*, 294 U.S. 1 (1935) 2, 16, 21

Teva Pharms. USA, Inc. v. *Pfizer, Inc.*, 395 F.3d 1324 (Fed. Cir. 2005) 20

Tilghman v. *Proctor*, 102 U.S. 707 (1880) 14, 15

United Carbon Co. v. *Binney & Smith Co.*, 317 U.S. 228 (1942) 14, 18

TABLE OF AUTHORITIES—Continued

Page

United States v. *Adams*, 383 U.S. 39 (1966) 21

Va. Military Inst. v. *United States*, 508 U.S. 946 (1993) 3

Valmont Indus., Inc. v. *Reinke Mfg. Co., Inc.*, 983 F.2d 1039 (Fed. Cir. 1993) 30

Warner-Jenkinson Co. v. *Hilton Davis Chem. Co.*, 520 U.S. 17 (1997) 5, 20, 21, 29

White v. *Dunbar*, 119 U.S. 47 (1886) 21

Winans v. *Denmead*, 56 U.S. 330 (1853) 21

Young v. *Lumenis, Inc.*, 492 F.3d 1336 (Fed. Cir. 2007) 6, 10, 13

STATUTES

Patent Act of 1952, Pub. L. No. 82-593, 66 Stat. 792:

35 U.S.C. § 112 ..... *passim*

35 U.S.C. § 221 20

35 U.S.C. § 271(e)(5) 20

35 U.S.C. § 285 28

Act of Apr. 10, 1790, 1 Stat. 109 ..... 4, 19

Act of Feb. 21, 1793, 1 Stat. 318 ..... 4, 19

Patent Act of July 4, 1836, 5 Stat. 119 ..... 5, 20

Patent Act of July 8, 1870, 16 Stat. 198 5

ADMINISTRATIVE MATERIALS

Manual of Patent Examining Procedures (8th ed. 2004):

§ 706.03(d) 15, 24

§ 2111 23

TABLE OF AUTHORITIES—Continued

Page

§ 2131 23

§ 2145 23

USPTO Patent Full-Text and Image Database, http://patft.uspto.gov/netahtml/PTO/search-adv.htm 26

OTHER AUTHORITIES

3 *Chisum on Patents* (2009) 4, 19

Oration Honouring David Christian Ward (1999), *available at* http://www.mun.ca/president/99-00report/honor/honorary_ward.html 7

IN THE

Supreme Court of the United States

NO. 10-426

APPLERA CORP. AND TROPIX, INC.,

Petitioners,

v.

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., AND YALE UNIVERSITY,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

---

BRIEF IN OPPOSITION

PRELIMINARY STATEMENT

The petition in this case is premised on the mistaken notion that the "claims" of a patent issued by the U.S. Patent and Trademark Office ("PTO") should operate as blueprints for circumventing the rights of inventors. But "the certainty which the law requires in patents is not greater than is reasonable." *Minerals Separation* v. *Hyde*, 242 U.S. 261, 270 (1916). Thus, "[e]xpressions quite as indefinite as 'high' and 'substantial,' in describing an invention or discovery, in patent specifications and claims, have been recognized by this court as sufficient."

Eibel Process Co. v. *Minn. & Ontario Paper Co.*, 261 U.S. 45, 66 (1923). Indeed, this Court has *never* invalidated patent claims simply because they are amenable to two reasonable constructions. To the contrary, "if the claim were fairly susceptible of two constructions, that should be adopted which will secure to the patentee his actual invention." *Smith* v. *Snow*, 294 U.S. 1, 14 (1935). Consistent with (and in reliance on) those holdings, inventors have for decades sought and obtained patents with claim terms like "substantially," "approximately," and "about." In view of this Court's precedents and decades of reliance on those precedents, *stare decisis* answers the question presented. See *Hilton* v. *S.C. Pub. Rys. Comm'n*, 502 U.S. 197, 206-207 (1991); *Payne* v. *Tennessee*, 501 U.S. 808, 828 (1991). That alone is sufficient reason to deny the petition.

Largely ignoring this Court's precedents, petitioners urge that the standard of "definiteness" allegedly employed by the decision below conflicts with the statutory requirement of distinct and particular claims. But the standard they assail—which suggests a claim is indefinite if it is "insolubly ambiguous"—was invoked nowhere by the decision below. Rather, that decision held that the claims were not indefinite because "those skilled in the art would understand what is claimed," Pet. App. 11a, a standard petitioners nowhere challenge.

Besides, petitioners misread the Patent Act. The language petitioners invoke was inserted to require applicants to clearly distinguish their inventions not from the universe of potentially infringing activities but rather from *other* subject matter disclosed in the patent that is *not* being claimed as the novel and useful invention. See *Merrill* v. *Yeomans*, 94 U.S. 568, 570 (1876). Thus, an inventor must state what the invention "is": Where the invention is part of a machine or composition of matter that combines the old with the new, the inventor must

identify what parts of the machine or composition constitute the claimed invention. But petitioners' proposal that claims must mark unmistakable boundaries for what the invention is "not" lacks foundation. Indeed, it is impossible to reconcile with the "doctrine of equivalents," which gives patentholders the right to exclude others from practicing not only what is expressly defined by the claims but also "all equivalents." That doctrine "renders the scope of patents less certain" but is needed to preserve the value of the patent. *Festo Corp.* v. *Shoketsu Kinzoku Kogy Kabushiki Co.*, 535 U.S. 722, 732 (2002). In any event, the patent in this case distinctly points out the invention being claimed; the purported ambiguity petitioners invoke is not one that would lead to reasonable confusion.

The assertion of importance likewise fails. For more than a decade, the Federal Circuit has addressed indefiniteness under settled standards without criticism by its active judges. While the standard differs from the one the PTO applies to applications, patent examination and patent enforcement are different. The PTO has explained that its rules are designed to force applicants to amend and improve their claims during an interactive patent examination process. Courts, by contrast, must either accept or invalidate patents the PTO has already approved. Regardless, both the PTO and Federal Circuit agree that the disputed claim language here satisfies statutory requirements.

Finally, this case is an entirely unsuitable vehicle for addressing the question presented. The decision's interlocutory posture "alone furnishe[s] sufficient ground for the denial" of the petition. *Hamilton-Brown Shoe Co.* v. *Wolf Bros. & Co.*, 240 U.S. 251, 258 (1916); see *Va. Military Inst.* v. *United States*, 508 U.S. 946 (1993) (Scalia, J., concurring). And this case does not present a genuine issue of indefiniteness. Petitioners object to a

single segment of a novel class of molecules that are otherwise claimed with definite structural specificity. That disputed piece, a "linkage group" that does not "substantially interfere" with hybridization, defines a boundary the public would never seek to approach, because hybridization is *necessary* to the function of those molecules. The indefiniteness challenge is thus based on the phony premise that petitioners want to figure out, with certainty, how to avoid the patent by building a molecule that, because it has obstructed hybridization, is effectively broken from the outset.

STATEMENT

I. STATUTORY BACKGROUND

The Patent Acts of 1790 and 1793 required inventors to "distinguish" their inventions from "other things before known." Act of Apr. 10, 1790, ch. 7, §2, 1 Stat. 109; Act of Feb. 21, 1793, ch. 11 §3, 1 Stat. 318. Neither expressly required inventors to distinguish those inventions using "claims." See *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 379 (1996).[1] In this country, the practice of using "claims" to assist in identifying the invention derived from *Evans* v. *Eaton*, 20 U.S. 356 (1822). See 3 *Chisum on Patents* §8.02[1] (2009). In that case, the Court addressed whether subject matter must be identified as inventive or whether novelty "may be established by comparing the machine specified in the patent with former machines in use." 20 U.S. at 433. Construing the 1793 Act's requirement that inventors "distinguish" their inventions from prior art, the Court held that the Act did not authorize a patent "[w]hich

---

[1] Patent practitioners typically refer to the numbered paragraphs, set forth at the end of U.S. Patents, as the "claims." The written description of the invention that appears before the separately numbered claims, together with the claims themselves, is referred to as the "specification."

describes the machine fully and accurately, as a whole, mixing up the new and old, but does not *in the slightest degree* explain what is the nature or limit of the improvement which the party claims as his own." *Id.* at 434 (emphasis added).

From that decision, "claim" practice—the practice of identifying the part of a machine, process, etc., that is claimed as novel and patentable in numbered "claims"—has developed. The practice received statutory recognition in the Patent Act of July 4, 1836, ch. 357, § 6, 5 Stat. 119, see *Markman*, 517 U.S. at 379, which required an inventor to "particularly specify and point out the part, improvement, or combination which he claims as his own invention or discovery." Such "claims" provide "notice" of what in the patent constitutes the "new" and patentable invention, as opposed to the "old" and nonpatentable material surrounding it. As this Court explained, the 1836 Act "very wisely require[d] of the applicant a distinct and specific statement of what he claims to be new" since "in every application for a patent, the descriptive part is necessarily largely occupied with what is not new." *Merrill*, 94 U.S. at 570. The Patent Act of 1870 carried forward that purpose, requiring the inventor to "particularly point out and distinctly claim the part, improvement, or combination which he claims as his invention or discovery." Act of July 8, 1870, ch. 230, § 26, 16 Stat. 198. And the 1952 Patent Act, which states that a patent's specification shall include "one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention," 35 U.S.C. § 112, "is not materially different from the 1870 Act with regard to claiming, reissue, and the role of the PTO," *Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 26 (1997).

The Patent Act imposes additional requirements that add to the concreteness and clarity of patents. For ex-

ample, the specification must contain "a written description of the invention, and of the manner and process of making and using it." 35 U.S.C. §112; see *Ariad Pharms., Inc.* v. *Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (en banc). That description must be "in such full, clear, concise, and exact terms *as to enable any person* skilled in the art * * * *to make and use the [invention].*" 35 U.S.C. §112 (emphasis added). That requirement is known as "enablement." See *CFMT, Inc.* v. *YieldUP Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003).

In *Markman*, this Court held that the construction of patent claims is "an issue for the judge not the jury." 517 U.S. at 391. As a result, federal courts now conduct specialized "*Markman*" hearings to determine the scope of patent claims. Because the question of what a claim means is inextricably bound up with the issue of indefiniteness—the notion that the claim does not sufficiently set forth what it covers—the Federal Circuit has recognized that indefiniteness "is a matter of claim construction," *Praxair, Inc.* v. *ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008), to which "general principles of claim construction apply," *Young* v. *Lumenis, Inc.*, 492 F.3d 1336, 1346 (Fed. Cir. 2007). The Federal Circuit thus has ruled that claims are indefinite unless "those skilled in the art would understand what is claimed." *Ibid.*

II. Proceedings Below

A. The Invention

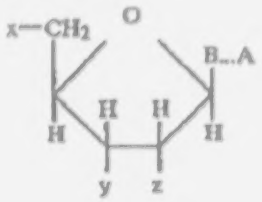
Labeled nucleotides are used in a variety of applications, including DNA sequencing and diagnosing hereditary diseases. Because each DNA sequence "pairs," "binds," or "hybridizes" predictably with the complementary DNA sequence (so AA-TT hybridizes with TT-AA), labeled nucleotides can be used to detect, monitor, localize, or isolate specific nucleic acid sequences (*e.g.*, DNA

sequences), even in small quantities. Pet. App. 3a. For example, a laboratory seeking a particular DNA sequence could introduce a so-called "probe" of the complementary DNA sequence made of labeled nucleotides. Any unhybridized material is later removed. The laboratory then looks for the labeled nucleotides. If they remain—having hybridized with the complementary DNA sequence—that indicates that the DNA sequence being tested for was present in the sample. See *ibid.*

Traditionally, labeled nucleotides were prepared by radioactive methods—*i.e.*, nucleotide sequences were marked by exposing them to radioactive materials, making them radioactive as well. While that made it possible to "see" them, it had many drawbacks. Radioactive nucleotides are potentially hazardous, and thus expensive and inconvenient to transport, use, and store. Pet. App. 3a-4a.

Dr. David Ward and co-workers at Yale University revolutionized the field by preparing chemically-labeled DNA molecules that still function like DNA. Previously, chemical labels (*e.g.*, fluorescent dyes) were not considered acceptable for marking DNA because it was generally assumed that structural modification to incorporate such a label would compromise the molecule's ability to function as DNA. But Dr. Ward synthesized a series of novel nucleotide derivatives that solved the problem. As one observer described it, his invention "can light up our genes in a kaleidoscope of colours and make them glow," an innovation involving "the physics of optics, computational science, digital imaging, microscopy, molecular biotechnology and cell biology." *Oration Honouring David Christian Ward* (1999), *available at* http://www.mun.ca/president/99-00report/honor/honorary_ward.html. For that groundbreaking invention, Dr. Ward was inducted into the National Academy of Sciences.

This case concerns patents arising out of that path-marking invention. U.S. Patent No. 5,449,767 ("the '767 Patent") sets forth one aspect of Dr. Ward's invention. It defines "an oligo- or polynucleotide containing a nucleotide" of the following structure:



'767 Patent col. 3, C.A. App. 169 (App., *infra*, 6a). The central 5-member ring is a sugar "moiety" or segment. "B" denotes a base (either a 7-deazapurine or a pyrimidine) attached to a specific place on the sugar ring. "A" denotes the label (*e.g.*, the dye). The label A is attached to the base B at a specific position defined by the claim. The patent describes the invention—and the nature and properties of each element in the diagram—at length. The general description of the invention spans two pages, and the detailed description of the invention spans twelve. See '767 Patent cols. 3-30, C.A. App. 169-182 (App., *infra*, 6a-19a). To design labeled DNA outside the claimed invention's scope, one would simply attach the label to a different, unclaimed position on the base B or to the sugar.

In questioning the patent's definiteness, petitioners do not contend that the base, the sugar, or the label are inadequately defined. Instead, they attack a small piece of the molecule, the "linkage group" (depicted as a dotted line in the formula) that connects the base and label. Per the claim, the linkage group "does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to hybridize with a nucleic acid." See '767 Patent col. 31, C.A. App. 183 (App., *infra*, 31a). The petition urges that the description does not sufficiently

define "substantially" to allow someone to avoid infringement. But the petition nowhere explains why anyone would want to circumvent the patents by designing a linkage group that *does* interfere with the hybridization process. Such a molecule would be useless in any application that requires the modified DNA to function as "natural" DNA, *i.e.*, it would be contrary to the invention's very purpose of producing labeled DNA that functions just like unlabeled DNA.

The PTO specifically considered virtually indistinguishable claim language. Pet. App. 16a. The '767 Patent issued from a chain of applications, including Application Serial No. 496, 415. In a March 21, 1986 Supplemental Amendment, the applicants claimed a "linkage group not interfering substantially with the characteristic ability of A to form a stable complex with avidin." C.A. App. 4270-4271 (App., *infra*, 24a, 25a, 28a). The examiner initially rejected that language as "indefinite," and requested a structural definition. *Id.* at 4284 (App., *infra*, 38a). In response, the applicants explained why structural language would not adequately define their invention. *Id.* at 4306-4307 (App., *infra*, 40a-44a). Agreeing, the examiner "withdrew the indefiniteness objection," Pet. App. 16a, and the next office action limited indefiniteness concerns to misspellings and other formalities. *Id.* at 4323 (App., *infra*, 47a).

B. The District Court's Decision

Following a *Markman* hearing, the district court construed the disputed "linkage group" language along with other claims language. Pet. App. 7a, 39a.[2] Petitioners then moved for summary judgment, asserting that the invention was anticipated by prior art and failed to

---

[2] The claims construction ruling is not included in the petition appendix but is publicly available as No. 3:04cv929 (JBA), 2006 U.S. Dist. Lexis 74570 (D. Conn. Oct. 12, 2006).

comply with the written description, enablement, and claim definiteness requirements of 35 U.S.C. § 112. Pet. App. 35a.

The court denied summary judgment on petitioners' enablement and written description defenses, finding disputed issues of material fact. Pet. App. 40a-51a. The district court invalidated some claims as anticipated by prior art. *Id.* at 61a-73a. Finally, the court found Dr. Ward's "linkage group" indefinite based primarily on the views of petitioners' expert, rejecting the contrary views of respondents' expert. *Id.* at 55a-58a. Ignoring Dr. Ward's extensive guidance for selecting linkage groups, the district court looked instead for an exact, numerical standard of "substantial interference." *Id.* at 54a-61a. Finding none, the court held the patents indefinite.

C. The Federal Circuit's Decision

The Federal Circuit affirmed in part and reversed in part. Turning to indefiniteness first, the court of appeals unanimously held that the claim terms were sufficiently definite. Pet. App. 10a-18a.

The court explained that resolving an "indefiniteness" claim "requires a determination whether those skilled in the art would understand what is claimed." Pet. App. 11a (quoting *Young* v. *Lumenis, Inc.*, 492 F.3d 1336, 1346 (Fed. Cir. 2007)). In this case, the court explained, one skilled in the art would understand the meaning of the phrase "not interfering substantially" because, among other things, there were dependent claims in the patent that identified specific linkage groups. Pet. App. 14a. Citing longstanding precedent, the court explained that a person of ordinary skill in the art would understand "the term 'not interfering substantially'" in the challenged claims as "allow[ing] for at least as much interference as that exhibited" using the particular "linkage group * * * specified in the dependent claims." *Ibid.* Additional ex-

amples of linkage groups were found elsewhere in the specification, along with "criteria for selecting among them." *Id.* at 15a. Dr. Ward provided examples of tests performed on particular linkage groups, identifying specific results that were deemed "acceptable." *Id.* at 15a-16a. Those examples also taught that a polynucleotide's "thermal denaturation profile" (essentially, a comparison of the melting point of labeled hybrids to unmodified material) can be used to measure the degree to which a linkage group interferes with hybridization. *Id.* at 15a. Finally, looking to the patent's "prosecution history," the decision below found still more examples of linkage groups that did not substantially interfere. *Id.* at 16a.

The court did not mention the extrinsic testimony the district court cited as evidence of indefiniteness. Instead, it ruled that "the intrinsic evidence here provides 'a general guideline and examples sufficient to enable a person of ordinary skill in the art to determine [the scope of the claims],' *In re Marosi*, 710 F.2d 799, 803 (Fed. Cir. 1983)." Pet. App. 16a-17a (brackets in original). A "person of ordinary skill in the art," the court concluded, could "look to the thermal denaturation and hybridization (including T_m) profiles to see if they fall within the range of exemplary values disclosed in the intrinsic evidence." *Id.* at 17a.

The Federal Circuit was not asked to pass on, and did not pass on, any dispute regarding proper construction of the "linkage group." Nonetheless, the court *sua sponte* modified that construction as to one of the patents, and on that basis, found it anticipated by prior art. Pet. App. 13a, 26a-27a. As to the other two Ward patents, the court found disputed issues of material fact, reversed summary judgment on anticipation grounds, and "remanded for further proceedings consistent with" its opinion. *Id.* at 21a-26a, 33a.

Although Judge Plager joined the panel's unanimous opinion, he dissented from denial of rehearing en banc. Pet. App. 75a-79a. No other judge joined him.

REASONS FOR DENYING THE PETITION

The decision below does not conflict with any decision of this Court, PTO examination practice, or any statutory text. The assertion of importance is unfounded. The case's interlocutory posture is by itself reason for denying review in favor of a case with a fully developed record. And the case in any event does not properly present the question on which petitioners seek review.

I. The Decision Below Does Not Conflict With Any Decision Of This Court Or Statutory Text

Petitioners' assertion of conflict is based on a mistaken premise. This Court has never held that patent claims must mark the exact boundaries separating the invention from all potential infringements. Rather, the law requires only the certainty that is "reasonable" under the circumstances. This Court thus has upheld as "sufficient" expressions "quite as indefinite as 'high' and 'substantial,' in describing an invention or discovery, in patent specifications and claims." *Eibel Process Co.* v. *Minn. & Ontario Paper Co.*, 261 U.S. 45, 66 (1923).

The Court has required the patent to define the boundaries between the claimed invention and other, non-novel subject matter disclosed in the application. But the Court has never suggested that claims must also chart safe harbors for potential infringers by describing in detail everything the invention is not. Petitioner's contrary view—that patent claims cannot brook any ambiguity—cannot be reconciled with this Court's precedents. It defies this Court's longstanding requirement that courts "construe" a claim with two possible meanings by adopting a construction that preserves the inventor's rights. And it is inconsistent with this Court's

adherence to the doctrine of equivalents which, by definition, affords patentees rights beyond the literal claims of a patent.

A. The Federal Circuit Correctly Applied This Court's Precedents Permitting Relative Terms Like "Substantially"

1. Petitioners and their *amici* ignore this Court's longstanding recognition that "the certainty which the law requires in patents is not greater than is reasonable, having regard to their subject matter." *Minerals Separation* v. *Hyde*, 242 U.S. 261, 270 (1916). Consistent with that principle, inventors may assert claims using "[e]xpressions quite as indefinite as 'high' and 'substantial.'" *Eibel Process*, 261 U.S. at 66. To avoid indefiniteness, the inventor need not provide an exact description. Instead, given the "large class of substances and the range of treatment within the terms of the claims," it is permissible for inventors to "leav[e] something to the skill of persons applying the invention" so long as the claims are "sufficiently definite to guide those skilled in the art to its successful application." *Mineral Separation*, 242 U.S. at 271.

In this case, the Federal Circuit followed that formula. Resolving an "indefiniteness" claim, the court noted, requires "a determination whether those skilled in the art would understand what is claimed." Pet. App. 11a (quoting *Young* v. *Lumenis, Inc.*, 492 F.3d 1336, 1346 (Fed. Cir. 2007), in turn quoting *Datamize, LLC* v. *Plumtree Software, Inc.*, 417 F.3d 1342, 1348 (Fed. Cir. 2005)). Ignoring the standard actually applied below, petitioners assail the notion that the claim must be "insolubly ambiguous" to be indefinite. See Pet. i, 3, 4, 15, 19, 23. But that gloss is never mentioned by the decision below. Besides, any gloss must take meaning from the standard applied below and this Court's cases—*i.e.*, the claim is "insolubly ambiguous" only when "those

skilled in the art," upon examining the claim in light of their knowledge and other disclosures in the patent, "would [not] understand what is claimed."

The court of appeals properly applied those principles. Although the claim itself uses relative terms ("substantially interferes") in describing unacceptable linkage groups, the court identified disclosures throughout the patent—including "dependent claims," examples and discussion in the patent's specification, and particular examples of suitable linkages in the prosecution history—that would allow one skilled in the art to determine the permissible degree of interference. See pp. 10-11, *supra*. The patent, the court held, would "allow for at least as much interference as that exhibited" by the identified "linkage group[s]." Pet. App. 14a; see also 15a-16a. This Court's cases regularly follow a similar course, evaluating the claim in light of the rest of the patent. See *Eibel Process*, 261 U.S. at 65-66; *United Carbon Co.* v. *Binney & Smith Co.*, 317 U.S. 228, 235-236 (1942); *Gen. Elec. Co.* v. *Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938).

Petitioners overlook longstanding precedent allowing inventors to claim with relative words of degree like "substantially." The term "maintained at a substantial elevation" has been sustained against an indefiniteness challenge. *Eibel Process*, 261 U.S. at 65. Claims to a rubber-curing process including the step of "heating said mold to a temperature range approximating a predetermined rubber curing temperature" were held patentable. *Diamond* v. *Diehr*, 450 U.S. 175, 181 (1981). And Alexander Graham Bell's pioneering telephony patent, which claimed "[t]he method of, and apparatus for, transmitting vocal or other sounds telegraphically, as herein described, by causing electrical undulations, *similar in form to* the vibrations of the air," was upheld. *Dolbear* v. *Am. Bell Tel. Co.*, 126 U.S. 1, 163 (1888)

(emphasis added). So too were claims to "the manufacturing of fat acids and glycerides from fatty bodies by the action of water at a high temperature and pressure." *Tilghman* v. *Proctor*, 102 U.S. 707, 721 (1880). In none of those cases did the relative claim language fix the "metes and bounds" of the invention, as petitioners would demand. See Pet. 2. Instead, the claims would have to be construed in light of the rest of the patent.[3]

Petitioners' opposition to relative terms, moreover, is inconsistent with established PTO practice. The PTO's Manual of Patent Examining Procedure ("MPEP") instructs examiners to reject "relative" terms like "substantially" as indefinite *only* when "the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." MPEP § 706.03(d) (8th ed. 2004). That instruction comports with the Federal Circuit's approach here: The court upheld the use of the relative term "substantially interfere" because the specification (including dependent claims) allowed one of ordinary skill in the art to determine the tolerable degree of interference. That sort of careful, context-specific analysis pervades similar Federal Circuit cases.[4]

---

[3] While *Diehr*, *Dolbear*, and *Tilghman* did not address indefiniteness, this Court regularly resolves patent cases on grounds other than those raised by the parties. See *Permutit Co.* v. *Graver Corp.*, 284 U.S. 52 (1931) (petition raising novelty issues resolved on indefiniteness grounds); *Dann* v. *Johnston*, 425 U.S. 219 (1976) (addressing "obviousness" where question presented was directed to the patentability of the subject matter).

[4] See, *e.g.*, *Andrew Corp.* v. *Gabriel Elecs., Inc.*, 847 F.2d 819 (Fed. Cir.) ("substantially"), cert. denied, 488 U.S. 927 (1988); *Quantum Corp.* v. *Rodime, PLC*, 65 F.3d 1577 (Fed. Cir. 1995) ("approximately"), cert. denied, 517 U.S. 1167 (1996); *Exxon Research & Eng'g* v. *United States*, 265 F.3d 1371 (Fed. Cir. 2001) ("substan-

Petitioners' view also defies other settled principles. For example, the Court's decision in *Markman* teaches that ambiguous claim terms must be construed by the court. 517 U.S. at 387-388. Correspondingly, *Smith* teaches that courts should adopt constructions that save rather than invalidate the patent so as to "secure to the patentee his actual invention." 294 U.S. at 14. Such efforts would be pointless if the ambiguity that necessitated the act of construction would render the patent indefinite in any event, as petitioner assumes and one of its *amici* insists. See Pet. 18-19; Altera Br. 10-11.[5] Finally, petitioners' view cannot be reconciled with *Festo Corp.* v. *Shoketsu Kinzoku Kogy Kabushiki Co.*, 535 U.S. 722, 732 (2002), which upholds the "doctrine of equivalents." Under that doctrine, "the scope of the patent is not limited to its literal terms but instead embraces all equivalents to the claims described." *Ibid.* While that necessarily "renders the scope of patents less certain," this Court has recognized that it represents "the price of ensuring the appropriate incentive for innovation, and has affirmed the doctrine over dissents that urged a more certain rule." *Ibid.* *Festo* forecloses petitioners' view that the "claims" language must mark the precise boundaries of the inventor's rights.

---

tial"); *Deering Precision Instruments, LLC* v. *Vector Distribution Sys., Inc.*, 347 F.3d 1314 (Fed. Cir. 2003) ("substantially"), cert. denied, 540 U.S. 1184 (2004); *Ortho-McNeil Pharm., Inc.* v. *Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321 (Fed. Cir. 2007) ("about").

[5] Petitioner's suggestion that Federal Circuit practice allows vague constructions to substitute for vague claim language is not well-founded. That court can and has invalidated patents where the construction is vague. See, *e.g.*, *Halliburton Energy Servs., Inc.* v. *M-I LLC*, 514 F.3d 1244, 1251 (Fed. Cir. 2008) ("Even if a claim term's definition can be reduced to words, the claim is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully precise claim scope.").

The Federal Circuit's longstanding approach to indefiniteness is thus firmly grounded in this Court's cases. It is therefore little surprise that, for at least a decade, the Federal Circuit has applied its settled standards in multiple cases heard by multiple panels without a single dissent by an active judge. Judge Plager's dissent from denial of rehearing en banc appears to be a solitary view.

2. Petitioners' contrary theory, moreover, derives from a misreading of this Court's precedents. According to petitioners, patent claims must clearly distinguish the invention from anything and everything not infringing. But petitioner cannot identify a *single case* in which this Court has invalidated claims based on indefiniteness because the claims, although capable of reasonable construction, did not provide potential infringers with a blueprint for designing around the patent. Instead, petitioners' cases address patents that mixed the new invention with pre-existing machines or inventions and failed to distinguish adequately between the claimed innovation and the "old" or pre-existing art.

For example, in *Wabash Appliance*, the Court observed that Congress, "[r]ecognizing that most inventions represent improvements on some existing article, process, or machine, and that the description of the invention must in large part set out what is old in order to facilitate the understanding of what is new," appropriately "require[d] of the applicant 'a distinct and specific statement of what he claims to be new, and to his invention.'" 304 U.S. at 368-369. The patent before it, the Court held, failed to "adequately set out 'what he claims to be new'" because its description of the invention also "serve[d] aptly to describe the product of earlier manufacture." *Id.* at 369-370. "The failure of the patentee to make claim to a distinct improvement" over the prior art therefore doomed the claim. *Id.* at 370. Similarly, in *United Carbon*, the Court was concerned about "the

somewhat indeterminate character of the advance claimed to have been made" because the prior art patents "describe[d] products" that, "if not identical" to the claimed invention, were "at least of confusing similarity." 317 U.S. at 237.

Finally, the claims in *Permutit Co.* v. *Graver Corp.*, 284 U.S. 52 (1931), were not even ambiguous. Instead, the Court found the disclosures inadequate because, while the inventor claimed his invention improved on prior art by using a "free" zeolite bed combined with "rising space" above the bed, the patent's claims did not mention either feature. *Id.* at 57. The Court acknowledged that drawings attached to the patent showed both features, and that such "drawings * * * may be used as an aid to interpreting the specification or claim," but it concluded that they were "of no avail" there given the "entire absence of description of the alleged invention or a failure to claim it." *Id.* at 60. Here, by contrast, every feature of the claimed invention is set forth in the claims, and the patent's specification resolves any ambiguity.

B. The Federal Circuit's Definiteness Standard Does Not Conflict With The Patent Statute

Petitioners also assert (at 16-18) that the Federal Circuit's standard is inconsistent with the Patent Act's requirement that the specification contain "a written description of the invention" and "one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112. But petitioners ignore the origins of those requirements. The claim must "particularly point out" what the invention *is* by distinguishing the invention from other subject matter disclosed in the written description. A claim that is subject to construction does precisely that. The statute does not require the patent to delineate what the claim *is not* so as to distinguish the invention from every conceivable potential infringement.

Here, a person skilled in the art would fully have understood the nature of the invention.

1. As explained in greater detail above, see pp. 4-6, *supra*, the language in §112 derives from a series of decisions of this Court insisting *not* that the patent set forth a blueprint for circumvention but rather that it distinguish the new invention being claimed from preexisting art. This Nation's first two patent laws (the Patent Acts of 1790 and 1793) required inventors to "distinguish" their inventions from "other things before known," but made no mention of "claims" per se. See Act of Apr. 10, 1790, ch. 7, §2, 1 Stat. 109; Act of Feb. 21, 1793, ch. 11 §3, 1 Stat. 318. Instead, claims practice derived from *Evans* v. *Eaton*, 20 U.S. 356 (1822), which addressed whether subject matter must be identified as inventive, or whether instead novelty "may be established by comparing the machine specified in the patent with former machines in use." *Id.* at 433; see 3 *Chisum on Patents* §8.02[1] (2009). Construing the 1793 Patent Act, the Court held that the Act did not authorize a patent "[w]hich describes the machine fully and accurately, as a whole, mixing up the new and old, but does not *in the slightest degree* explain what is the nature or limit of the improvement which the party claims as his own." 20 U.S. at 433 (emphasis added).

Since then, this Court's cases have recognized that, because patents representing "improvements on some existing article" often must describe the new improvement together with the preexisting device, inventors must distinctly and specifically state what they "claim[ ] to be new." *Wabash*, 304 U.S. at 378-379. That requirement was incorporated into the Patent Act of July 4, 1836, ch. 357, §6, 5 Stat. 119, see *Markman*, 517 U.S. at 379, which required the inventor to "particularly specify and point out the part, improvement, or combination which he claims as his own invention or discovery." The

Court thus explained how the 1836 Act "very wisely require[d] of the applicant a distinct and specific statement of what he claims to be new" since "in every application for a patent, the descriptive part is necessarily occupied with what is not new." *Merrill*, 94 U.S. at 570. Similar language appeared in the 1870 Act. See p. 5, *supra*. And the 1952 Patent Act, which placed the claim definiteness requirement in its current form, "is not materially different from the 1870 Act with regard to claiming." *Warner-Jenkinson*, 520 U.S. at 26. The Act thus requires "notice" of what the invention "is" in the sense of distinguishing it from preexisting machines or prior art also described in the patent. But there is no requirement that it specify all means of infringement.

2. Petitioners' contrary arguments are premised almost entirely on the court-made doctrine that the claims "define" the invention. Pet. 16.[6] As an initial matter, that doctrine has never had the absolute quality petitioners attribute to it. For example, the doctrine of equivalents gives inventors rights beyond the literal terms of the claims. See p. 3, *supra*. Under that doctrine, "a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention." *Warner-Jenkinson*, 520 U.S. at 25-26; cf. *Winans* v. *Denmead*, 56 U.S. 330, 342 (1853) (infringement not limited to "the precise forms * * * described, but all other forms which embody [the] invention."). This Court has speci-

---

[6] The statutory definition of infringement, 35 U.S.C. § 221, did not even mention claims until 2003, when a declaratory judgment remedy was created for generic drug makers. See 35 U.S.C. § 271(e)(5); *Teva Pharms. USA, Inc.* v. *Pfizer, Inc.*, 395 F.3d 1324, 1334 (Fed. Cir. 2005).

fically rejected the notion that the doctrine of equivalents is inconsistent with § 112's requirement that the invention be identified with appropriate clarity. See *Warner-Jenkinson*, 520 U.S. at 25-26. That doctrine forecloses the notion that the claims themselves must specifically identify all infringing activities.

Besides, even if the claims "define" the invention, this Court has not confined its infringement analysis to the claims language. This Court regularly looks to other portions of the patent when construing claim terms. *United States* v. *Adams*, 383 U.S. 39, 49 (1966) ("[I]t is fundamental that claims are to be construed in the light of the specifications and both are to be read with a view to ascertaining the invention."); *White* v. *Dunbar*, 119 U.S. 47, 60 (1886) (looking to "the context of the specification" to determine whether it supported "giv[ing] the claim so broad a construction"); *Permutit Co.*, 284 U.S. at 60 (attached "drawings * * * may be used as an aid to interpreting the * * * claim"). Prior art may help define the claim, counseling a relatively broader or narrower construction. *Eibel Process*, 261 U.S. at 63; *Smith*, 294 U.S. at 14 ("the character of the patent and its commercial and practical success are such as to entitle the inventor to broad claims and to a liberal construction of those which he has made"). Infringement too may be judged by reference to "the mechanism described in the specification." *Fuller* v. *Yentzer*, 94 U.S. 288, 293 (1876). The decision below did no more than what this Court's cases allow—holding the relevant claims language, when read in connection with the remainder of the patent, sufficiently definite to guide one reasonably skilled in the art.

C. There Is No Conflict Between The Federal Circuit And The PTO

Petitioners assert (at 14-15) a conflict between the Federal Circuit's standard of indefiniteness and the

standard used by the PTO's Board of Patent Appeals ("BPAI") in processing patent applications. Petitioners note that the BPAI may "requir[e] the applicant to more precisely define the metes and bounds of the claimed invention by holding the claim unpatentable" when "a claim is amenable to two or more plausible claim constructions." Pet. 14 (internal quotation marks omitted). But petitioners overlook *why* the PTO will issue rejections under that more expansive standard. As the Board explained in *Ex Parte Miyazaki*, 89 U.S.P.Q.2d 1207 (BPAI 2008), the PTO applies a different standard in the application process "because the applicant has *an opportunity* and a duty *to amend the claims during prosecution* to more clearly and precisely define the metes and bounds of the claimed invention." *Id.* at 1211-1212 (emphasis added). But once the patent has been issued and infringement is being litigated, there is no opportunity to amend. For courts, the options are enforcing the patent or invalidating it.

The PTO's decision to apply a different standard thus does not reflect a disagreement with the Federal Circuit or a different construction of §112. It reflects the fact that, when the application is before the PTO, "claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed." *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989). The Federal Circuit likewise has never faulted the PTO's standard. "It would be inconsistent with the role assigned to the PTO in issuing a patent," the Federal Circuit has observed, "to require it to interpret claims in the same manner as judges who, post-issuance, operate under the assumption the patent is valid." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Because the "process of patent prosecution is an interactive one," examiners may insist on amendments to obtain the greatest clarity

possible. *Ibid.* But judicial decisions on validity are binary—the patent is either invalidated or upheld. *Ibid.*

Indeed, the PTO and the Federal Circuit regularly apply different standards in myriad contexts in light of their different roles:

- Before a patent issues, the PTO will give claims their "broadest reasonable interpretation" in light of the specification, MPEP, *supra*, §2111, to force applicants to amend them by narrowing and clarifying, *In re Zletz*, 893 F.2d at 321. "During litigation determining validity or infringement, however, this approach is inapplicable." *Atlantic Thermoplastics Co.* v. *Faytex Corp.*, 970 F.2d 834, 846 (Fed. Cir. 1992). Instead, courts give claims their most natural construction. *Ibid.*

- Before a patent issues, patent examiners who make out a *prima facie* case of obviousness will assign the applicant the burden of *disproving* obviousness. See MPEP, *supra*, §2131. After a patent issues, the burden of proving the patent "obvious" in litigation always remains on the party challenging the patent's validity. See *Sanofi-Synthelabo* v. *Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008).

- Before a patent issues, the PTO can require an applicant invoking commercial success as evidence of non-obviousness to provide hard evidence of success and a nexus to novelty. See MPEP, *supra*, §2145. Once the patent is issued, a *prima facie* case is established whenever a successful product is claimed in the patent, and the opposing party has the burden of disproving it. See *Demaco Corp.* v. *F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988).

- Before a patent issues, the PTO can force the applicant to provide a "satisfactory showing" that its claim of inventorship is correct if a publication names inventors other than those identified in the application. *In re Katz*, 687 F.2d 450, 455 (C.C.P.A. 1982). After a patent issues, the party alleging misjoinder must prove it "by clear-and-convincing evidence." See *Eli Lilly & Co.* v. *Aradigm Corp.*, 376 F.3d 1352, 1358 (Fed. Cir. 2004).

- Before a patent issues, a specification must be accepted as compliant with the enablement requirement of § 112, "unless there is reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971). After a patent issues, the accused infringer is free to dispute whether the specification enables. See *Amgen, Inc.* v. *Chugai Pharm. Co., Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991).

Petitioners' charge of "conflict" thus ignores the fact that PTO examination standards and judicial enforcement standards often diverge, and properly so, in light of the PTO's and the courts' distinct roles; the fact that the PTO can and should require amendment, while courts can only invalidate; and the fact that no presumption of validity attaches to a patent application before the PTO, but does attach once the patent issues.

There is no conflict, moreover, between the PTO and the Federal Circuit on the proper result here. The PTO, like this Court and the Federal Circuit, recognizes that relative terms like "substantial" are permissible so long as sufficient guidance can be discerned from the specification. See p. 15, *supra*; MPEP, *supra*, § 706.03(d). And both the PTO and the Federal Circuit agreed that the standard of definiteness was met here. The PTO examiner approved the application here only after his

concerns about the definiteness of virtually identical language were overcome. See Pet. App. 16a; p. 9, *supra*. The Federal Circuit, examining the same materials presented to the examiner, likewise agreed that the standard of definiteness was met. Pet. App. 13a-16a. This Court can hardly resolve a supposed conflict between two bodies on the standard of definiteness in a case where both bodies reached the identical conclusion that the definiteness requirement was met. This Court "'reviews judgments, not statements in opinions.'" *California* v. *Rooney*, 483 U.S. 307, 311 (1987) (quoting *Black* v. *Cutter Labs.*, 351 U.S. 292, 297 (1956)).

II. The Request For Further Review Falls Short of Justification

Petitioners have failed to demonstrate that this issue is important. For a decade, the Federal Circuit has employed its current standards without meaningful dispute or dissent. Before addressing petitioners' specific claims, however, we pause to point out precisely what petitioners are asking the Court to do. For almost a century, this Court has authorized the use of "[e]xpressions quite as indefinite as 'high' and 'substantial.'" *Eibel Process*, 261 U.S. at 66. In reliance on that and other precedents, patent applicants routinely seek and obtain patents with claim language like "substantially," "about," and "approximately"—terms that necessarily do not have a definite meaning standing by themselves, but rather gather their meaning from the context of the rest of the patent, such as the written description, the specification, charts and figures, working and/or prophetic examples, and descriptions of specific embodiments.

The PTO allows the use of such terms when the surrounding materials are sufficient. Indeed, even petitioners and their *amici* have relied on them. Since 1976, Applera has been assigned 102 patents that use the term "substantially," Yahoo has 25, Google has 34, Cisco Sys-

tems or its subsidiary has 479, Microsoft has 758, and General Motors has 3,047.[7] That word, "substantially," necessarily requires construction: It can "denote either language of approximation or language of magnitude" and does not in and of itself answer *how close* or *"how much."* Pet. App. 13a, 14a. *Amici* can urge that all those patents "have been prosecuted in compliance with the Patent Act" nonetheless, Altera Br. 1, only because nothing in the Patent Act imposes on inventors the draconian standards of definiteness petitioners advocate. In any event, given the overwhelming reliance on this Court's approval of relative claim terms in cases like *Eibel Process*, *stare decisis* weighs heavily against an effort to overturn them. See pp. 2, 14-15, *supra*. Such a tectonic upheaval in the Court's construction of a statute should not be contemplated absent a compelling need.

Petitioners have established no such need. Notwithstanding decades of application by myriad panels in myriad cases, the Federal Circuit's standards drew no serious dissents until Judge Plager's lone dissent in this case. That renders any claim of importance highly suspect. *Amici* cite an article quoting anonymous "experts in claim drafting" for the proposition that claims can be vaguely worded intentionally. Altera Br. 13. But *amici* do not show that the advice of those unidentified "experts" is followed. Nor should it have any effect: The PTO has authorized its examiners to *reject* any claim amenable to two or more constructions. *Ex Parte Miyazaki*, 89 U.S.P.Q.2d at 1209. Here, moreover, the applicants did not choose the disputed claim language to render the patent vague. As they explained to the PTO's

---

[7] Based on the Advanced Search feature of the PTO's website as of November 4, 2009. See http://patft.uspto.gov/netahtml/PTO/search-adv.htm.

satisfaction, the language was the most accurate definition of the invention possible. See p. 9, *supra*.

Asserting that the Federal Circuit's standard materially alters litigation outcomes, *amici* characterize one paper as showing that, in district court, patentee success rates on indefiniteness challenges "increased by sixty percentage points" between 1998 and 2008. Altera Br. 11 (citing Christa J. Laser, *A Definite Claim on Claim Indefiniteness*, 11 Chi.-Kent J. Intell. Prop. 25 (2010)). But *amici* fail to mention that the same article found that patentee success rates before the Federal Circuit fell precipitously in the last data point of the article's already small data set. Laser, *supra*, at 33, Fig. 2. That finding undermines their supposed "trend." Far from being "toothless," the definiteness requirement remains a powerful tool that has disposed of substantial infringement cases. See, *e.g.*, *Acacia Media Techs. Corp.* v. *New Destiny Internet Group*, No. 05-CV-114, MDL Case No. 05-1665, (N.D. Cal. Oct. 23, 2009) (granting summary judgment in multi-district case involving five patents and 45 defendants), *aff'd*, No. 2010-1081 (Fed. Cir. Oct. 7, 2010); *Quantum Corp.*, 65 F.3d at 1580-1584. And the assault on suits filed by non-practicing entities ("NPEs") is baseless. In the vast majority of cases taken to judgment, the accused infringer wins. Altera Br. 16 n.6.[8] Any NPE "problem" should be remedied by, for example, liberalizing the Patent Act's fee-shifting provision, 35 U.S.C. §285, not by radically changing the law of definiteness to the detriment of Nobel laureates, National Academy inductees, and other contributors to the useful arts and sciences.

---

[8] Like all research universities, respondent Yale University is expanding knowledge rather than selling products. NPEs like Yale have made countless contributions to the useful arts and sciences, including the invention asserted in the Ward patents.

Finally, *amici* urge that the Federal Circuit's reversal rate on claims-construction issues proves that claims are excessively ambiguous because district courts allegedly "get[] it wrong nearly half the time." Altera Br. 8. But the reported reversal rates cannot account for the inherent selection bias resulting from rational litigants appealing only relatively close cases, leaving the cases where the district court has clearly "gotten it right" unappealed. Indeed, petitioners did just that here, declining to appeal the district court's construction of the linkage group.[9] The reversal rate may also reflect that claim construction "is a special occupation, requiring, like all others, special training and practice," *Markman*, 517 U.S. at 388, and the Federal Circuit's tendency, as a specialist court that reviews claims construction *de novo*, to see things differently than generalist district courts. In any event, petitioners have not demonstrated that the process is unworkable, that skilled judges cannot ascertain the scope of most patents, or that any issues that do arise are a product of patent quality as opposed to the immense scientific and technological complexity of many inventions. Nor have they shown that, to the extent any problem exists, it should be "solved" by invalidating more patents for indefiniteness as opposed to addressing the Federal Circuit's method of claims construction.

In any event, petitioners' unsubstantiated attempt to radically revise claims practice is misdirected. This Court decided *Eibel Process* in 1923, and Congress overhauled the patent laws in 1952. If Congress had thought the sort of claims language authorized by *Eibel*

---

[9] *Amicus* Yahoo challenges the result in the *Bright Response* case. Yahoo Br. 14-16. While that may be an unfortunate example of a district court (actually a magistrate judge) "getting it wrong," one erroneous decision from a non-Article III judge hardly justifies this Court's intervention.

Process improper, it would have placed corrective language in the 1952 Act. See *Hilton*, 502 U.S. at 202. Far from doing so, Congress carried forward the relevant language of the 1870 Act into the 1952 Patent Act, which "is not materially different from the 1870 Act with regard to claiming, reissue, and the role of the PTO." *Warner-Jenkinson*, 520 U.S. at 26. If petitioners have a complaint about that decision, their remedy lies with Congress. Indeed, unlike this Court, Congress could legislate prospectively to avoid upsetting the public's reliance on this Court's longstanding acceptance of terms like "substantially" in appropriate contexts.

III. The Decision Below Is A Poor Vehicle

Finally, this case represents an inadequate vehicle for further review. First, notwithstanding petitioners' claim that the PTO and the Federal Circuit have adopted different standards for definiteness, both the PTO and the Federal Circuit agreed that these claims were sufficiently definite. The claims also passed muster with Judge Plager, who voted with the original panel that found them definite. His dissent from rehearing takes issue with the governing standard, but nowhere suggests that the claims here would be invalid under a plausible alternative.[10] Review premised on a purported disagreement between the PTO and the Federal Circuit should await a case in which they actually disagree. See pp. 24-25, *supra*. While petitioners also object (at 27-28) to certain "functional" claim language, that argument was neither pressed in district court nor addressed in the court of appeals. This Court is "a court of review, not of first view," and traditionally does not address issues that

---

[10] Indeed, while claiming indefiniteness in the Federal Circuit, petitioners abandoned any effort to challenge the district court's construction of the claim. This case thus involves a claim with just one reasonable construction.

were not preserved or addressed below. *Cutter* v. *Wilkinson*, 544 U.S. 709, 719 n.7 (2005).[11]

The petition, moreover, does not properly present the issue it purports to raise. The invention here allows nucleotides to be "labeled" without interfering with their ability to function as DNA, *i.e.*, to "hybridiz[e]" in the same fashion as unlabeled DNA. It establishes a specific and concrete chemical structure to achieve that result. Thus, when first confronted with the allowed claims of the '767 Patent, petitioners sent a letter to the Assistant Commissioner of Patents demonstrating that they fully understood what the claims covered—"fluorescently labeled DNA sequencing fragments." C.A. App. 2793 (App., *infra*, 51a).

Petitioners nonetheless seize on one small part of the novel nucleotide derivative at issue, a "linkage" group that does not "substantially interfere" with hybridization. Pet. 9. According to petitioners, the patent fails to mark the boundaries of the invention because it does not clearly distinguish non-infringing nucleotides with linkage groups that *do* substantially interfere with hybridization from infringing molecules that do not. But petitioners never explain why anyone would deliberately label a nucleotide such that hybridization is obstructed; the whole point of the invention and the prior art of radiologically labeled nucleotides was to mark the nucleotides without affecting their ability to hybridize. Petitioners thus seek to invalidate a patent based on the notion that they cannot clearly ascertain a claims "boun-

---

[11] The 1952 Patent Act specifically allows functional claim language, overruling the precedent petitioners cite. See *Valmont Indus., Inc.* v. *Reinke Mfg. Co., Inc.*, 983 F.2d 1039, 1042 (Fed. Cir. 1993). Had petitioners' objection been presented to the district court, it could have been addressed by construing the disputed language in accordance with the functional claiming provision of § 112.

dary" no reasonable person would approach. In essence, they assert that the patent is invalid because it does not tell them how to build around it by making a molecule that would not work.

Because patents are a quid-pro-quo in which the government awards an exclusivity period in exchange for disclosing the invention, *Kewanee Oil Co.* v. *Bicron Corp.*, 416 U.S. 470, 484 (1974), the Patent Act does require the patent to describe the invention and its use "in such full, clear, concise, and exact terms *as to enable any person* skilled in the art * * * *to make and use [it]*," 35 U.S.C. § 112 (emphasis added). If the patent does not "enable" others to build the invention, it is invalid. Pet. App. 14a n.4. But petitioners do not assert in this Court that the patent did not enable them to practice the invention. Instead, they assert that the patent is indefinite because the claim language, standing alone, does not clearly define a nucleotide with obstructed hybridization that would not work anyway.

Finally, the decision below is interlocutory—it merely remands the case for further proceedings. That alone is grounds for denying review, *Hamilton-Brown Shoe Co.* v. *Wolf Bros. & Co.*, 240 U.S. 251, 258 (1916), particularly in a case that, like this one, could use further factual development. On remand, petitioners presumably will present multiple challenges to the patents' validity, including challenges based on prior art. They may challenge enablement. As the foregoing discussion and petitioners' own submissions make clear, all of these issues are interrelated. See Pet. 22-23 n.9 (criticizing the Federal Circuit's holding that the defenses of anticipation and indefiniteness are mutually exclusive); Yahoo Br. 8-9 (arguing that some patent linkage group examples cited by the Federal Circuit are found in the prior art). If the question presented is to be reviewed at all, it should be reviewed in a case with a fully developed

record following a final judgment disposing of all related issues. And if this issue has the importance petitioners claim—and it does not—such a case will surely arise in due course. Review at this time is premature.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

JEFFREY A. LAMKEN
MARTIN V. TOTARO
MOLOLAMKEN LLP
The Watergate, Suite 660
600 New Hampshire Ave., NW
Washington, D.C. 20037
(202) 556-2000

MICHAEL HAWES
Counsel of Record
L. GENE SPEARS
AARON STREETT
BAKER BOTTS LLP
One Shell Plaza
910 Louisiana Street
Houston, Texas 77002-4995
(713) 229-1750
michael.hawes@bakerbotts.com

Counsel for Respondents

November 2010

APPENDIX

US005449767A

United States Patent [19]

Ward et al.

[11] Patent Number: 5,449,767

[45] Date of Patent: * Sep. 12, 1995

[54] MODIFIED POLYNUCLEOTIDES AND METHODS OF PREPARING SAME

[75] Inventors: **David C. Ward**, Guilford, Conn.; **Penninn R. Langer**, Monsey, N.Y.; **Alexander A. Waldrop, III**, Charlottesville, Va.

[73] Assignee: **Yale University**, New Haven, Conn.

[*] Notice: The portion of the term of this patent subsequent to Dec. 8, 2004 has been disclaimed.

[21] Appl. No.: 886,660

[22] Filed: May 20, 1992

Related U.S. Application Data

[60] Continuation of Ser. No. 130,002, Dec. 8, 1987, abandoned, which is a division of Ser. No. 496,915, May 23, 1983, Pat. No. 4,711,955, which is a continuation-in-part of Ser. No. 255,223, Apr. 17, 1981, abandoned.

[51] Int. Cl.[6] C07H 21/00

[52] U.S. Cl. 536/24.3; 536/25.32; 536/25.6; 536/26.6

[58] Field of Search 536/24.3, 25.32, 25.6, 536/26.6; 435/6

[56] References Cited

U.S. PATENT DOCUMENTS

3,328,389 6/1967 Shimizu et al. 260/211.5

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

070685 1/1983 European Pat. Off. .
70687 1/1983 European Pat. Off. .

(List continued on next page.)

OTHER PUBLICATIONS

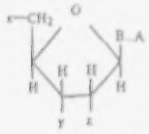
Trayer et al., "Preparation of Aderosine Nucleotide Derivatives Suitable for Affinity Chromatography", *Biochem. J.* (1974) 139:609–623.

(List continued on next page.)

Primary Examiner—Che S. Chereskin
Attorney, Agent, or Firm—Ronald C. Fedus; John L. Santalone

[57] ABSTRACT

Compounds having the structure:

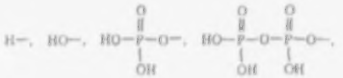


wherein B represents 7-deazapurine, or pyrimidine moiety covalently bonded to the $C^{1'}$-position of the sugar moiety, provided that when B is 7-deazapurine, it is attached at the N^9-position of the 7-deazapurine and when B is pyrimidine, it is attached at the N^1-position;

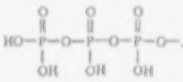
wherein A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded ribonucleic acid, deoxyribonucleic acid duplex, or DNA-RNA hybrid;

wherein the dotted line represents a chemical linkage joining B and A, provided that if B is 7-deazapurine, the linkage is attached to the 7-position of the deazapurine, and if B is pyrimidine, the linkage is attached to the 5-position of the pyrimidine; and

wherein each of x, y and z represents



or



either directly, or when incorporated into oligo- and polynucleotides, provide probes which are widely useful.

71 Claims, No Drawings

U.S. PATENT DOCUMENTS

3,337,510	8/1967	Hanze	260/211.5
3,338,882	8/1967	Wechter	260/211.5
3,804,826	4/1974	Schelt et al.	260/211.5 R
3,893,998	7/1975	Secrist, III et al.	260/211.5 R
3,915,958	10/1975	Shuman et al.	260/211.5 R
3,917,383	11/1975	Meyer et al.	260/211.5 R
3,960,840	6/1976	Secrist, III et al.	260/211.5 R
3,968,101	7/1976	Christensen et al.	260/211.5
4,008,363	2/1977	Re et al.	536/28
4,038,480	7/1977	Robins et al.	536/27
4,048,307	9/1977	Yokota et al.	424/180
4,067,774	1/1978	Rubenstein et al.	195/63
4,086,417	4/1978	Ishida et al.	536/29
4,088,639	5/1978	Zappelli et al.	260/112.5 R
4,096,324	6/1978	Kelly et al.	536/23
4,134,792	1/1979	Boguslaski et al.	195/99
4,151,349	4/1979	Traeger et al.	536/28
4,171,432	10/1979	Carrico et al.	536/26
4,213,893	7/1980	Carrico et al.	260/112.5
4,228,237	10/1980	Hevey et al.	435/7
4,230,698	10/1980	Bobek et al.	424/180
4,230,797	10/1980	Boguslaski et al.	435/7
4,247,544	1/1981	Bergstrom et al.	424/180
4,261,893	4/1981	Boguslaski et al.	260/326 N
4,267,171	5/1981	Bergstrom et al.	424/180
4,302,204	11/1981	Wahl et al.	23/230.3
4,318,980	3/1982	Boguslaski et al.	435/7
4,318,981	3/1992	Bard et al.	435/7
4,318,982	3/1982	Hornby et al.	435/7
4,355,165	10/1982	Boguslaski et al.	544/237
4,358,535	11/1982	Falkow et al.	435/5
4,363,759	12/1982	Boguslaski et al.	260/112.7
4,374,925	2/1983	Litman et al.	435/7
4,380,580	4/1983	Boguslaski et al.	435/7
4,383,031	5/1983	Boguslaski et al.	435/7
4,446,231	5/1984	Self	435/7
4,469,863	9/1984	Ts'o et al.	536/27
4,581,333	4/1986	Kourilsky et al.	

FOREIGN PATENT DOCUMENTS

2618419	11/1976	Germany	
2618511	11/1976	Germany	
3045375	7/1982	Germany	
18-24191	10/1943	Japan	16 E/611.2
58-62194	4/1983	Japan	
1548741	7/1979	United Kingdom	
1552607	9/1979	United Kingdom	
2019408	10/1979	United Kingdom	
2026690	2/1980	United Kingdom	
1564578	4/1980	United Kingdom	
2034323	6/1980	United Kingdom	
2041922	9/1980	United Kingdom	
2045239	10/1980	United Kingdom	
2125964	3/1984	United Kingdom	
8302276	7/1983	WIPO	
8302277	7/1983	WIPO	
8302286	7/1983	WIPO	

OTHER PUBLICATIONS

Broker, et al. (Feb. 1978) Nucleic Acids Research 5:363–383.

Tekman, et al Journal of Biological Chemistry (Nov. 1960), Vol. 235:3254–3259.

Bergstrom, D. E. and Ruth, J. L., "Synthesis of C-5 Substituted Pyrimidine Nucleosides via Organopalladium Intermediates", JACS 98:6, 1587–1588 (1976).

Bigge, C. F. "Synthesis of 5-Styryl Derivatives of Uracil Nucleosides and Nucleotides", Tetrahedron letters, 19, 1653–1656 (1979).

Bayley et al., Methods in Enzymology, vol. 46, 69–114 (1977).

E. A. Bayer and M. Wilchek, "The Use of the Avidin-Biotin Complex as a Tool in Molecular Biology," in *Methods of Biochemical Analysis*, 26, pp. 1–45 (1980).

D. Bergstrom and M. Ogawa, "C-5 Substituted Pyrimidine Nucleosides. 2". Synthesis Via Olefin Coupling To Organopalladium Intermediates Derived From Uridine and 2'-Deoxyuridine, *J. Am. Chem. Soc.*, 100, pp. 8106–8112 (1978) [Bergstrom I].

D. Bergstrom and J. L. Ruth, "Properties of C-5 Mercurated Pyrimidine Nucleosides," *J. Carbohydrates, Nucleotides and Nucleosides*, 4, pp. 257–289 (1977) [Bergstrom II].

C. F. Bigge et al., "Palladium-Catalyzed Coupling Reactions of Uracil Nucleosides and Nucleotides," *J. Am. Chem. Soc.*, 102, pp. 2033–2038 (1980).

C. Brandon et al., "Structure of a New Pyrimidine from *Bacillus Subtilis* Phage SP-15 Nucleic Acid", *Nature New Biology*, 239, pp. 70–71 (1972).

T. R. Broker et al., "Electron Microscopic Visualization Of tRNA Genes with Ferritin-Avidin: Biotin Labels," *Nucl. Acids Res.*, 5, pp. 363–383 (1978).

R. M. K. Dale et al., "Direct Covalent Mercuration of Nucleotides and Polynucleotides," *Biochemistry*, 14, pp. 2447–2457 (1975) [Dale I].

M. Ya. Feldman, *Reactions of Nucleic Acids and Nucleoproteins With Formaldehyde*, ...Ed. (19...).

J. L. Guesdon et al., "The Use of Avidin-Biotin Interaction In Immunoenzymatic Techniques", *J. Histochem. and Cytochem.* 27, pp. 1131–1139 (1979).

OTHER PUBLICATIONS

H. Hayashi and K. Nakanishi, "Synthesis and Absolute Configuration of (+)-5-(4',5'-Dihydroxypentyl)uracil from *Bacillus Subtilis* Phage SP-15 Deoxyribonucleic Acid," *J. Am. Chem. Soc.*, 95, pp. 4081-4083 (1973) [Hayashi I].

H. Hayashi et al. "Structure and Synthesis of Dihydroxypentyluracil from Bacteriophage SP-15 Deoxyribonucleic Acid," *J. Am. Chem. Soc.*, 95, pp. 8749-8757 (1973) [Hayashi II].

P. R. Langer et al., "Enzymatic Synthesis of Biotin-Labeled Polynucleotides: Novel Nucleic Acid Affinity Probes", *Proc. Natl. Acad. Sci. USA*, 78, pp. 6633-6637 (1981) [Langer I].

P. R. Langer and D. C. Ward, "A Rapid and Sensitive Immunological Method For In Situ Gene Mapping," in *Developmental Biology Using Purified Genes*, ed. D. D. Brown, Academic Press, pp. 647-658 (1981) [Langer II].

P. R. Langer and D. C. Ward, Abstract 1153. "A Rapid and Sensitive Immunological Method For In Situ Gene Mapping," in Journal of Supramolecular Structure and Cellular Biology, ed. Alan R. Liss, Inc. (1981) [Langer III].

Manning et al., "A Method for Gene Enrichment Based on the Avdin-Biotin Interaction. Application to the *Drosophila* Ribosomal RNA Genes," *Biochemistry*, 16, pp. 1364-1370 (1977) [Manning I].

M. Pellegrini et al., "Application of the Avidin-Biotin Method of Gene Enrichment to the Isolation of Long Double-Strande DNA Containing Specific Gene Sequences", *Nucl. Acids Res., 4, pp. 2961-2973 (1977).*

J. L. Ruth and D. E. Bergstrom, "C-5 Substituted Pyrimidine Nucleosides. I. Synthesis of C-5 Allyl, Propyl, and Propenyl Uracil and Cytosine Nucleosides via Organopalladium Intermediates," *J. Org. Chem.*, 43, pp. 2870-2876 (1978).

A. Sodja and N. Davidson, "Gene Mapping and Gene Enrichment by the Avidin-Biotin Interaction: Use of Cytochrome-C as a Polyamine Bridge," *Nucl. Acids Res.*, 5, pp. 383-*399* (1978).

M. Swierkowski and D. Shugar, "Poly 5-Ethyluridylic Acid, A Polyuridylic Acid Analogue", *J. Mol. Biol.*, 47, pp. 57-67 (1970).

J. G. J. Bauman et al., "A New Method for Fluorescence Microscopical Localization of Specific DNA Sequences by In Situ Hybridization of Fluorochrome-Labelled RNA", *Exp. Cell Res.*, 128, pp. 485-490 (1980) [Bauman I].

J. G. J. Bauman et al., "Rapid and High Resolution Detection of in situ Hybridisation to Polytene Chromosomes Using Fluorochrome-Labeled RNA," *Chromosoma* (Berl.) 84, pp. 1-18 (1981) [Bauman II].

D. Bergstrom and J. L. Ruth, "Preparation of C-5 Mercurated Pyrimidine Nucleosides," *J. Carbohydrates, Nucleotides and Nucleosides*, 4, pp. 251-269 (1977) [Bergstrom II].

R. M. K. Dale et al., "The Synthesis and Enzymatic Polymerization of Nucleotides Containing Mercury: Potential Tools for Nucleic Acid Sequencing and Structural Analysis", *Proc. Natl. Acad. Sci. USA*, 70, pp. 2238-2242 (1973) [Dale II].

W. S. Dallas and S. Falkow, "Molecular and Genetic Analysis of a DNA Sequence Encoding for Enterotoxin Snythesis in *Escherichia coli*," *Thirteenth Joint Conference on Cholera*, The U.S.-Japan Cooperative Medical Science Program (1979) [Dallas I].

W. S. Dallas et al., "The Characterization of an *Escherichia coli* Plasmid Determinant That Encodes for the Production of a Heat-Labile Enterotoxin," *Plasmids of Medical Environmental and Commercial Importance*, K. N. Timmis and A. Puhler, editors, Elsevier/North Holland Biomedical Press (1979) [Dallas II].

D. J. Eckermann and R. H. Symons, "Sequence at the Site of Attachment of an Affinity-Label Derivative of Puromycin on 23-S Ribosomal RNA of *Escherichia coli* Ribosomes," *Eur. J. Biochem.*, 82, pp. 225-234 (1978).

H. G. Gratzner, "Monoclonal Antibody to 5-Bromo- and 5-Iododeoxyuridine: A New Reagent for Detection of DNA Replication," *Science*, 218, pp. 474-475 (1982).

M. Grunstein and D. Hogness, "Colony Hybridization: A Method for the Isolation of Cloned DNAs That Contain a Specific Gene", *Proc. Natl. Acad. Sci. USA*, 72, pp. 3961-3965 (1975).

K. Hofmann et al., "Iminobiotin Affinity Columns And Their Application To Retrieval Of Streptanudin", *Proc. Natl. Acad. Sci. USA*, 77, pp. 4666-4668 (1980).

F. S. Huang and J. S. Pagano, "Nucleic Acid Hybridization Technology and Detection of Proviral Genomes," *Methods Virol.* 6, pp. 457-497 (1977).

A. M. Jeffrey et al., "Benzo[a] pyrene-Nucleic Acid Derivative Found In Vivo: Structure of a Benzo[a]-pyrenetetrahydrodiol Epoxide-Guanosine Adduct," *J. Am. Chem. Soc.*, 98, pp. 5714-5715 (1976).

R. G. Kallen et al., "The Occurrence of a New Pyrimidine Base Replacing Thymine in a Bacteriophage DNA: 5-Hydroxymethyl Uracil," *J. Mol. Biol.* 5, pp. 248-250 (1962).

D. E. Kennel, "Principles And Practices of Nucleic Acid Hybridization" Pro. Nucl. Acid Res., 11, 259-301 (1971).

M. Koreeda et al., "Alkylation of Polyguanylic Acid at the 2-Amino Group and Phosphate by the Potent Mutagen (±)-7β, 8α-Dihydroxy-9 β,10β epoxy —7,8,9,-10-tetrahydrobenzo[a]pyrene," *J. Am. Chem. Soc.*, 98, pp. 6720-6722 (1976).

OTHER PUBLICATIONS

T. T. Kuo et al., "5-Methylcytosine Replacing Cytosine in the Deoxyribonucleic Acid of a Bacteriophage for *Xanthomonas oryzae*," *J. Mol. Biol.*, 34, pp. 373-375 (1978).

I. R. Lehman and E. A. Pratt, "On the Structure of the Glucosylated Hydroxymethylcytosine Nucleotides of Coliphages T2, T 4 and T6," *J. Biol. Chem.* 235, pp. 3254-3259 (1960).

E. T. Maggio (ed.), *Enzyme-Immunoassay* (1980).

J. E. Manning et al., "A New Method Of in situ Hybridization," *Chromosoma* (Berl), 53, pp. 107-117 (1975) *Manning II*].

J. Marmur et al., "Unique Properties of nucleic Acid from *Bacillus Subtilis* Phage SP-15, *Nature New Biology*, 239, pp. 68-70 (1972).

T. W. Munns and M. K. Liszewski, "Antibodies Specific for Modified Nucleotides: An Immunochemical Approach for the Isolation and Characterization of Nucleic Acids," in *Progress in Nucleic Acid Research and Molecular Biology*, ed. W. E. Cohn, Academic Press, 24, pp. 109-165 (1980).

T. Nelson and D. Brutlag, "Addition of Homopolymers to the 3'—ends of Duplex DNA with Terminal Transferase," *Methods in Enzymology* (vol. 68) *Recombinant DNA, ed. R. Wu, pp. 41-50.*

J. Reiser et al., "Transfer of Small DNA Fragments From Polyacrylamide Gels to Diazobengyloxymethyl Paper and Detection by Hybridization with DNA Probes," Biochemical and Biophysical Research Communications, 85, pp. 1104-1112 (1978).

P. W. J. Rigby et al., "Labeling Deoxyribonucleic Acid to High Specific Activity In Vitro to Nick Translation with DNA Polymerase I," *J. Mol. Biol.*, 113, pp. 237-251 (1977).

G. T. Rudkin and R. D. Stollar, "High Resolution Detection of DNA-RNA Hybrids in situ by Indirect Immunofluorescence", *Nature*, 265, pp. 472-473 (1977).

M. So, "Characterization of an *Escherichia coli* Plasmid Encoding for the Synthesis of Heat-Labile Toxin: Molecular Cloning of the Toxin Determinant", *Infection and Immunity* 21, pp. 405-411 (1978).

Lubert Stryer, Biochemistry, 3rd ed., c. 1975, 1981, 1988 See p. 184, "Formation of an Enzyme-Substrate Complex is the First Step in Enzymatic Catalysis".

C.-Y. Lee et al. "8-(6-Aminohexyl)-Amino-Adenine Nucleotide Derivatives for Affinity Chromatography, "Arch. Biochem. Biophys. 163, pp. 561-569 (1974).

MODIFIED POLYNUCLEOTIDES AND METHODS OF PREPARING SAME

The invention disclosed and/or claimed in this application was made in the course of work carried out under grants from the Public Health Service, National Institute of General Medical Research Grant No. P50-GM20124; Public Health Service, National Cancer Institute Training Grant No. T32-CA09159; and Public Health Service, National Institute of General Medical Science Grant No. T32-GM07499. The Government has certain rights in the invention.

This is continuation of application Ser. No. 07/130,002, filed Dec. 8, 1987, now abandoned, which is in turn a division of application Ser. No. 06/496,915, filed May 23, 1983, issued Dec. 8, 1987 as U.S. Pat. No. 4,711,955. Application Ser. No. 06/496,915 is in turn a continuation of application Ser. No. 06/255,223, filed Apr. 17, 1981, now abandoned.

BACKGROUND OF THE INVENTION

Many procedures employed in biomedical research and recombinant DNA technology rely heavily on the use of nucleotide or polynucleotide derivatives radioactively labeled with isotopes of hydrogen (^{3}H), phosphorous (^{32}p), carbon (^{14}C), or iodine (^{125}I). Such radioactive compounds provide useful indicator probes that permit the user to detect, monitor, localize, or isolate nucleic acids and other molecules of scientific or clinical interest, even when present in only extremely small amounts. To date, radioactive materials have provided the most sensitive, and in many cases the only, means to perform many important experimental or analytical tests. There are, however, serious limitations and drawbacks associated with the use of radioactive compounds. First, since personnel who handle radioactive material can be exposed to potentially hazardous levels of radiation, elaborate safety precautions must be maintained during the preparation, utilization, and disposal of the radioisotopes. Secondly, radioactive nucleotides are extremely expensive to purchase and use, in large part due to the cost of equipment and manpower necessary to provide the appropriate safeguards, producer-/user health monitoring services, and waste-disposal programs. Thirdly, radioactive materials are often very unstable and have a limited shelf-life, which further increases usage costs. This instability results from radiolytic decomposition, due to the destructive effects associated with the decay of the radioisotope itself, and from the fact that many isotopes (e.g. ^{32}p and ^{125}I) have half-lives of only a few days.

It is known that haptens can combine with antibodies, but can initiate an immune response only if bound to a carrier. This property can be exploited in detection and identification testing.

It is also known that biotin and iminobiotin strongly interact with avidin, a 68,000 dalton glycoprotein from egg white. This interaction exhibits one of the tightest, non-covalent binding constants ($K_{diss} = 10^{-15}$) seen in nature. If avidin is coupled to potentially demonstrable indicator molecules, including fluorescent dyes, e.g. fluorescein or rhodamine, electron-dense reagents, e.g. ferritin, hemocyanin, or colloidal gold, or enzymes capable of depositing insoluble reaction products, e.g. peroxidase or alkaline phosphatase, the presence, location, or quantity of a biotin probe can be established. Although iminobiotin binds avidin less tightly than biotin, similar reactions can be used for its detection. Moreover, the reversibility of the iminobiotin-avidin interaction, by decreasing solution pH, offers significant advantages in certain applications.

The specificity and tenacity of the biotin-avidin complex has been used in recent years to develop methods for visually localizing specific proteins, lipids, or carbohydrates on or within cells (reviewed by E. A. Bayer and M. Wilchek in Methods of Biochemical Analysis, 26, 1, 1980). Chromosomal location of RNA has been determined by electron microscopy using a biotinized protein, cytochrome C, chemically crosslinked to RNA as a hybridization probe. The site of hybridization was visualized through the binding of avidin-ferritin or avidin-methacrylate spheres mediated by the avidin-biotin interaction. (J. E. Manning, N. D. Hershey, T. R. Broker, M. Pellegrini, H. K. Mitchell, and N. Davidson, Chromosoma, 53, 107, 1975; J. E. Manning, M. Pellegrini, and N. Davidson, Biochemistry, 61, 1364, 1977; T. R. Broker, L. M. Angerer, P. H. Yen, N. D. Hersey, and N. Davidson, Nucleic Acid Res., 5, 363, 1978; A. Sodja and N. Davidson, Nucleic Acid Res., 5, 383, 1978.) This approach to the detection of polynucleotide sequences, although successful in the specialized cases examined which were highly reiterated sequences, is not of general utility for analysis of polynucleotides present in single or low copy number.

Moreover, methods for attaching chemical moieties to pyrimidine and purine rings are known. Several years ago a simple and rapid acetoxymercuration reaction was developed for introducing covalently bound mercury atoms into the 5-position of the pyrimidine ring, the C-8 position of the purine ring or the C-7 position of a 7-deazapurine ring, both in nucleotides and polynucleotides. (R. M. K. Dale, D. C. Livingston and D. C. Ward, Proc. Natl. Acad. Sci. U.S.A., 70, 2238, 1973; R. M. K. Dale, E. Martin, D. C. Livingston and D. C. Ward, Biochemistry, 14, 2447, 1975.) It was also shown several years ago that organomercurial compounds would react with olefinic compounds in the presence of palladium catalysts to form carbon-carbon bonds (R. F. Heck, J. Am. Chem. Soc., 90, 5518, 1968; R. F. Heck, Ibid., 90, 5526, 1968; R. F. Heck, Ibid., 90, 5531, 1968; R. F. Heck, Ibid., 90, 5535, 1968; and R. F. Heck, J. Am. Chem. Soc. 91, 6707, 1969.) Bergstrom and associates (J. L. Ruth and D. E. Berstrom, J. Org. Chem., 43, 2870, 1978, and D. E. Bergstrom and M. K. Ogawa, J. Am. Chem. Soc., 100, 8106, 1978) and Bigge, et al. (C. F. Bigge, P. Kalantis, J. R. Deck and M. P. Mertes, J. Am. Chem. Soc., 102, 2033, 1980) have recently applied this reaction scheme in the synthesis of C-5 substituted pyrimidine nucleotide compounds.

Finally, it is known that antibodies specific for modified nucleotides can be prepared and used for isolating and characterizing specific constituents of the modified nucleotides. (T. W. Munns and M. K. Liszewski, Progress in Nucleic Acid Research and Molecular Biology, 24, 109, 1980.) However, none of the antibodies prepared to date against naturally occurring nucleotides have been shown to react with their nucleotide determinant when it exists in a double-stranded RNA or DNA duplex or when in DNA-RNA hybrid molecules.

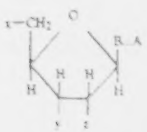
To circumvent the limitations of radioactively labeled probes or previously utilized chemical and biological probes, a series of novel nucleotide derivatives that contain biotin, iminobiotin, lipoic acid, and other determinants attached covalently to the pyrimidine or purine ring have been synthesized. These nucleotide deriva-

tives, as well as polynucleotides and coenzymes that contain them, will interact specifically and uniquely with proteins such as avidin or antibodies. The interaction between modified nucleotides and specific proteins can be utilized as an alternative to radioisotopes for the detection and localization of nucleic acid components in many of the procedures currently used in biomedical and recombinant-DNA technologies. Methods employing these modified nucleotide-protein interactions have detection capacities equal to or greater than procedures which utilize radioisotopes and they often can be performed more rapidly and with greater resolving power.

These new nucleotide derivatives can be prepared relatively inexpensively by chemical procedures which have been developed and standarized as discussed more fully hereinafter. More significantly, since neither the nucleotide probes of this invention nor the protein reagents employed with them are radioactive, the compounds can be prepared, utilized, and disposed of, without the elaborate safety procedures required for radioisotopic protocols. Moreover, these nucleotide derivatives are chemically stable and can be expected to have functional shelf-lives of several years or more. Finally, these compounds permit the development of safer, more economical, more rapid, and more reproducible research and diagnostic procedures.

SUMMARY OF THE INVENTION

Compounds having the structure

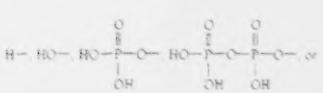


wherein B represents a purine, deazapurine, or pyrimidine moiety covalently bonded to the C^1-position of the sugar moiety, provided that when B is purine or 7-deazapurine, it is attached at the N^9-position of the purine or deazapurine, and when B is pyrimidine, it is attached at the N^1-position;

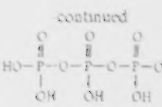
wherein A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded ribonucleic acid, deoxyribonucleic acid duplex, or DNA-RNA hybrid;

wherein the dotted line represents a chemical linkage joining B and A, provided that if B is purine the linkage is attached to the 8-position of the purine, if B is 7-deazapurine, the linkage is attached to the 7-position of the deazapurine, and if B is pyrimidine, the linkage is attached to the 5-position of the pyrimidine; and

wherein each of x, y, and z represents



continued

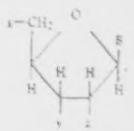


are widely useful as probes in biomedical research and recombinant DNA technology.

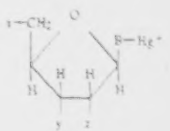
Particularly useful are compounds encompassed within this structure which additionally have one or more of the following characteristics: A is non-aromatic; A is at least C^5; the chemical linkage joining B and A includes an α-olefinic bond; A is biotin or iminobiotin; and B is a pyrimidine or 7-deazapurine.

These compounds may be prepared by a process which involves:

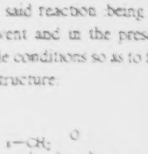
(a) reacting a compound having the structure:



with a mercuric salt in a suitable solvent under suitable conditions so as to form a mercurated compound having the structure:



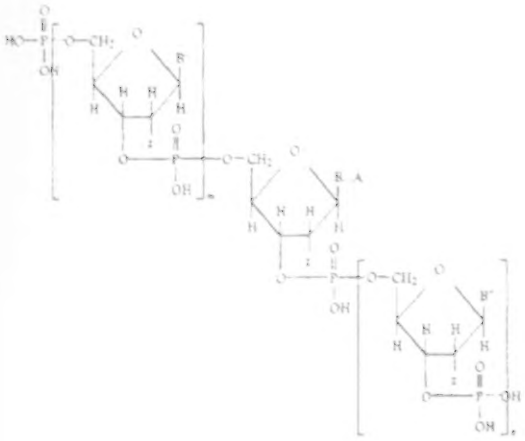
(b) reacting said mercurated compound with a chemical moiety reactive with the $-Hg^+$ portion of said mercurated compound and represented by the formula . . . N, said reaction being carried out in an aqueous solvent and in the presence of K_2PdCl_4 under suitable conditions so as to form a compound having the structure:



wherein N is a reactive terminal functional group or is A; and

(c) recovering said compound as said modified nucleotide when N is A, or when N is a reactive terminal group, reacting said compound with a compound having the structure M-A, wherein M represents a functional group reactive with N in an aqueous solvent under suitable conditions so as to form said modified nucleotide, which is then recovered.

This invention also provides compounds having the structure:



wherein each of B, B', and B'' represents a purine, 7-deazapurine, or pyrimidine moiety covalently bonded to the C^1-position of the sugar moiety, provided that whenever B, B', or B'' is purine or 7-deazapurine, it is attached at the N^9-position of the purine or 7-deazapurine, and whenever B, B', or B'' is pyrimidine, it is attached at the N^1-position;

wherein A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded duplex formed with a complementary ribonucleic or deoxyribonucleic acid molecule

wherein the dotted line represents a chemical linkage joining B and A, provided that if B is purine the linkage is attached to the 8-position of the purine, if B is 7-deazapurine, the linkage is attached to the 7-position of the deazapurine, and if B is pyrimidine, the linkage is attached to the 5-position of the pyrimidine;

wherein z represents H— or HO—; and

wherein m and n represent integers from 0 up to about 100,000

These compounds can be prepared by enzymatic polymerization of a mixture of nucleotides which include the modified nucleotides of this invention. Alternatively, nucleotides present in oligo- or polynucleotides may be modified using chemical methods.

Nucleotides modified in accordance with the practices of this invention and oligo- and polynucleotides into which the modified nucleotides have been incorporated may be used as probes in biomedical research, clinical diagnosis, and recombinant DNA technology. These various utilities are based upon the ability of the molecules to form stable complexes with polypeptides which in turn can be detected, either by means of properties inherent in the polypeptide or by means of detectable moieties which are attached to, or which interact with, the polypeptide.

Some uses include detecting and identifying nucleic acid-containing etiological agents, e.g. bacteria and viruses; screening bacteria for antibiotic resistance; diagnosing genetic disorders, e.g. thalassemia and sickle cell anemia; chromosomal karyotyping; and identifying tumor cells.

DETAILED DESCRIPTION OF THE INVENTION

Several essential criteria must be satisfied in order for a modified nucleotide to be generally suitable as a substitute for a radioactively-labeled form of a naturally occurring nucleotide. First, the modified compound must contain a substituent or probe that is unique, i.e., not normally found associated with nucleotides or polynucleotides. Second, the probe must react specifically with chemical or biological reagents to provide a sensitive detection system. Third, the analogs must be relatively efficient substrates for commonly studied nucleic acid enzymes, since numerous practical applications require that the analog be enzymatically metabolized, e.g., the analogs must function as substrates for nucleic acid polymerases. For this purpose, probe moieties should not be placed on ring positions that sterically, or otherwise, interfere with the normal Watson-Crick hydrogen bonding potential of the bases. Otherwise, the substituents will yield compounds that are inactive as polymerase substrates. Substitution at ring positions that alter the normal "anti" nucleoside conformation also must be avoided since such conformational changes usually render nucleotide derivatives unacceptable as polymerase substrates. Normally, such considerations limit substitution positions to the 5-position of a pyrimidine and the 7-position of a purine or a 7-deazapurine.

Fourth, the detection system should be capable of interacting with probe substituents incorporated into both single-stranded and double-stranded polynucleotides in order to be compatible with nucleic acid hybridization methodologies. To satisfy this criterion, it is preferable that the probe moiety be attached to the purine or pyrimidine through a chemical linkage or "linker arm" so that it can readily interact with antibodies, other detector proteins, or chemical reagents.

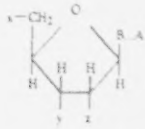
Fifth, the physical and biochemical properties of polynucleotides containing small numbers of probe substituents should not be significantly altered so that current procedures using radioactive hybridization

probes need not be extensively modified. This criterion must be satisfied whether the probe is introduced by enzymatic or direct chemical means.

Finally, the linkage that attaches the probe moiety should withstand all experimental conditions to which normal nucleotides and polynucleotides are routinely subjected, e.g., extended hybridization times at elevated temperatures, phenol and organic solvent extraction, electrophoresis, etc.

All of these criteria are satisfied by the modified nucleotides described herein.

These modified nucleotides have the structure

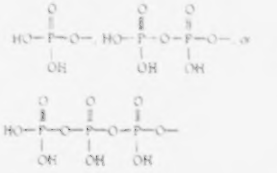


wherein B represents a purine, 7-deazapurine, or pyrimidine moiety covalently bonded to the $C^{1'}$-position of the sugar moiety, provided that when B is purine or 7-deazapurine, it is attached at the N^{9}-position of the purine or 7-deazapurine, and when B is pyrimidine, it is attached at the N^{1}-position;

wherein A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded ribonucleic acid, deoxyribonucleic acid duplex, or DNA-RNA hybrid;

wherein the dotted line represents a linkage group joining B and A, provided that if B is purine the linkage is attached to the 8-position of the purine, if B is 7-deazapurine, the linkage is attached to the 7-position of the deazapurine, and if B is pyrimidine, the linkage is attached to the 5-position of the pyrimidine; and

wherein each of x, y and z represents



These compounds are widely useful as probes in biomedical research and recombinant DNA technology.

Although in principal all compounds encompassed within this structural formula may be prepared and used in accordance with the practices of this invention, certain of the compounds are more readily prepared or used or both, and therefore are presently preferred.

Thus, although purines, pyrimidines and 7-deazapurines are in principal useful, pyrimidines and 7-deazapurines are preferred since purine substitution at the 8-position tends to render the nucleotides ineffective as polymerase substrates. Thus, although modified purines are useful in certain respects, they are not as generally useful as pyrimidines and 7-deazapurines. Moreover, pyrimidines and 7-deazapurines useful in this invention must not be naturally substituted at the 5-or 7- positions, respectively. As a result, certain bases such as thymine, 5-methylcytosine, and 5-hydroxymethylcytosine are not useful. Presently preferred bases are cytosine, uracil, deazaadenine and deazaguanine.

A may be any moiety which has at least three carbon atoms and is capable of forming a detectable complex with a polypeptide when the modified nucleotide is incorporated into a double-stranded duplex containing either deoxyribonucleic or ribonucleic acid.

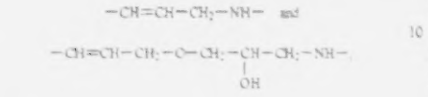
A therefore may be any ligand which possesses these properties, including haptens which are only immunogenic when attached to a suitable carrier, but are capable of interacting with appropriate antibodies to produce complexes. Examples of moieties which are useful include:

Of these the preferred A moieties are biotin and iminobiotin.

Moreover, since aromatic moieties tend to intercalate into a base-paired helical structure, it is preferred that the moiety A be nonaromatic. Also, since smaller moieties may not permit sufficient molecular interaction with polypeptides, it is preferred that A be at least C_5 so that sufficient interaction can occur to permit formation of stable complexes. Biotin and iminobiotin satisfy both of these criteria.

The linkage or group joining moiety A to base B may include any of the well known bonds including carbon-carbon single bonds, carbon-carbon double bonds, carbon-nitrogen single bonds, or carbon-oxygen single bonds. However, it is generally preferred that the chemical linkage include an olefinic bond at the α-position relative to B. The presence of such an α-olefinic bond serves to hold the moiety A away from the base when the base is paired with another in the well known double-helix configuration. This permits interaction with polypeptide to occur more readily, thereby facilitating complex formation. Moreover, single bonds with greater rotational freedom may not always hold the moiety sufficiently apart from the helix to permit recognition by and complex formation with polypeptide.

It is even more preferred that the chemical linkage group be derived from a primary amine, and have the structure —CH_2—NH—, since such linkages are easily formed utilizing any of the well known amine modification reactions. Examples of preferred linkages derived from allylamine and allyl-(3-amino-2-hydroxy-1-propyl) ether groups have the formulae



—CH=CH—CH_2—NH— and

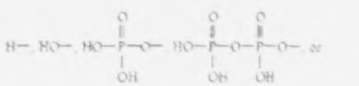
—CH=CH—CH_2—O—CH_2—CH(OH)—CH_2—NH—,

respectively.

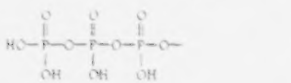
Although these linkages are preferred, others can be used, including particularly olefin linkage arms with other modifiable functionalities such as thiol, carboxylic acid, and epoxide functionalities.

The linkage groups are attached at specific positions, namely, the 5-position of a pyrimidine, the 8-position of a purine, or the 7-position of a deazapurine. As indicated previously, substitution at the 8-position of a purine does not produce a modified nucleotide which is useful in all the methods discussed herein. It may be that the 7-position of a purine, which is occupied by a nitrogen atom, could be the point of linkage attachment. However, the chemical substitution methods employed to date and discussed herein are not suitable for this purpose.

The letters x, y, and z represent groups attached to the 5', 3', and 2' positions of the sugar moiety. They may be any of



H—, HO—, HO—P(=O)(OH)—O—, HO—P(=O)(OH)—O—P(=O)(OH)—O—, or



Although conceivable, it is unlikely that all of x, y, and z will simultaneously be the same. More likely at least one of x, y, and z will be a phosphate-containing group, either mono-, di-, or tri-phosphate and at least one will be HO— or H—. As will be readily appreciated, the most likely identity of z will be HO— or H— indicating ribonucleotide or deoxyribonucleotide, respectively. Examples of such nucleotides include 5'-ribonucleoside monophosphates, 5'-ribonucleoside diphosphates, 5'-ribonucleoside triphosphates, 5'-deoxyribonucleoside monophosphates, 5'-deoxyribonucleoside diphosphates, 5'-deoxyribonucleoside triphosphates, 5'p-ribonucleoside-3'p, and 5'p-deoxyribonucleoside-3'p. More specific examples include modified nucleotides of this type in which A is biotin or iminobiotin, the chemical linkage is

—CH=CH—CH_2—NH— or

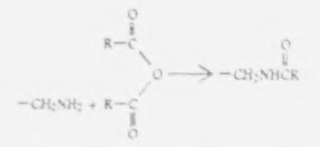
—CH=CH—CH_2—O—CH_2—CH(OH)—CH_2—NH—,

and B is uracil or cytosine.

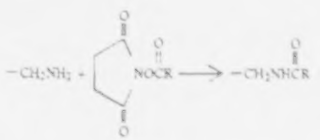
The general synthetic approach adopted for introducing the linker arm and probe moiety onto the base is discussed hereinabove. (See especially, J. L. Ruth and D. E. Bergstrom, Org. Chem., 43, 2870, 1978; D. E. Bergstrom and M. K. Ogawa, J. Amer. Chem. Soc. 100, 8106, 1978; and C. F. Bigge, P. Kalaritis, J. R. Deck and M. P. Mertes, J. Amer. Chem. Soc. 102, 2033, 1980.) However, the olefin substituents employed herein have not been used previously. To facilitate attachment of probe moiety A, it has been found particularly desirable to employ olefins with primary amine functional groups, such as allylamine [AA] or allyl-(3-amino-2-hydroxy-1-propyl) ether [NAGE], which permit probe attachment by standard amine modification reactions, such as,

$-CH_2NH_2 + R-C(=NH_2^+)-OR \longrightarrow -CH_2NHCR$

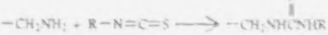
Imidate



Anhydride



NHS-ester (N-hydroxysuccinimide)



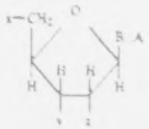
$-CH_2NH_2 + R-N=C=S \longrightarrow -CH_2NHCNHR$

Isothiocyanate

Epoxide

Because of ease of preparation it has been found preferable to use NHS-esters for probe addition. However, olefin linker arms with other modifiable functional groups, such as thiols, carboxylic acids, epoxides, and the like, can also be employed. Furthermore, both linker arm and probe can be added in a single-step if deemed desirable.

Specifically, modified nucleotides having the structure



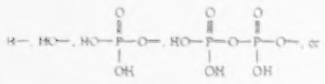
wherein B represents a purine, 7-deazapurine, or pyrimidine moiety covalently bonded to the C1'-posi-

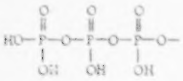
tion of the sugar moiety, provided that when B is purine or 7-deazapurine, it is attached at the N^9-position of the purine or deazapurine, and when B is pyrimidine, it is attached at the N^1-position;

wherein A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded ribonucleic acid, deoxyribonucleic acid duplex, DNA-RNA hybrid;

wherein the dotted line represents a chemical linkage joining B and A, provided that if B is purine, the linkage is attached to the 8-position of the purine, if 7-deazapurine, the linkage is attached to the 7-position of the deazapurine, and if B is pyrimidine, the linkage is attached to the 5-position of the pyrimidine; and

wherein each of x, y, and z represents

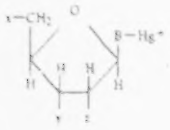




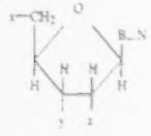
can be prepared by:

(a) reacting a compound having the structure:

with a mercuric salt in a suitable solvent under suitable conditions so as to form a mercurated compound having the structure:



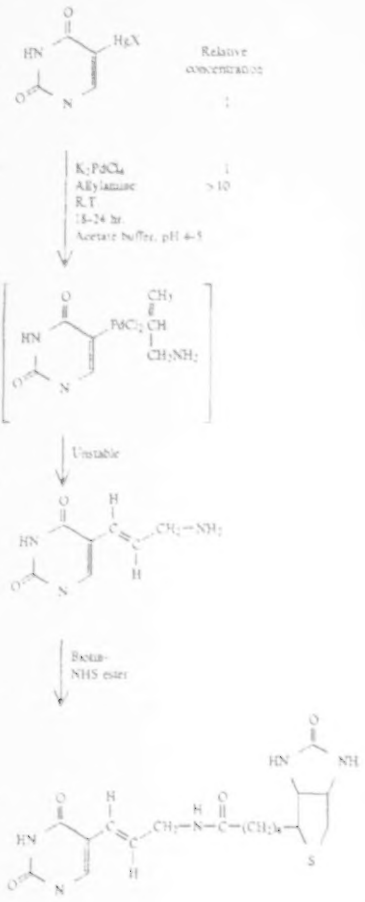
(b) reacting said mercurated compound with a chemical moiety reactive with the $-Hg^+$ portion, of said mercurated compound and represented by the formula . . . N, said reaction being carried out in an aqueous solvent and in the presence of K_2PdCl_4 under suitable conditions so as to form a compound having the structure:



wherein N is a reactive terminal functional group or is A, and

(c) recovering said compound as said modified nucleotide when N is A, or when N is a reactive terminal group, reacting said compound with a compound having the structure M-A, wherein M represents a functional group reactive with N in an aqueous solvent under suitable conditions, so as to form said modified nucleotide, which is then recovered.

The following schema is illustrative:



Although the reactions can be carried out at hydrogen ion concentrations as low as pH 1, or as high as pH 14, it is preferred to operate in the range from about 4 to 8. This is especially true when dealing with unstable compounds such as nucleoside polyphosphates, polynucleotides, and nucleotide coenzymes which are hydrolyzed at pH's outside this range. Similarly, it is preferred to operate at a temperature in the range from about 20° C. to 30° C. to avoid possible decomposition of labile organic substrates. However, the reactions can be carried out at temperatures from about 5° C. to 100° C. As

is usual with chemical reactions, higher temperatures promote the reaction rate and lower temperatures retard it. Thus, in the temperature range from 5° C. to 100° C., the optimum reaction time may vary from about 10 minutes to 98 hours. In the preferred temperature range, reaction times normally vary from about 3 to 24 hours.

The preferred procedure for maintaining the pH in the desired range is through the use of buffers. A variety of buffers can be employed. These include, for example, sodium or potassium acetate, sodium or potassium citrate, potassium citrate-phosphate, tris-acetate and borate-sodium hydroxide buffers. The concentration of buffer, when employed, can vary over a wide range, up to about 2.0 molar.

While a particular advantage of the mercuration and palladium catalyzed addition reactions is that they can be carried out in water, small amounts of an organic solvent can be usefully included as a solubility aid. The organic solvents usually chosen are those which are miscible with water. These may be selected from ethers, alcohols, esters, ketones, amides, and the like such as methanol, ethanol, propanol, glycerin, dioxane, acetone, pyridine and dimethylformamide. However, since it has been observed that the presence of alcohols, such as methanol, often results in alkoxy-addition across the olefin double bond, any organic solvent used as a solubility aid should be chosen carefully. Introduction of alkoxy substituents to the α- or β-exocyclic carbon atoms often results in the production of compounds which are utilized much less efficiently as enzyme substrates.

Although various mercuric salts may be utilized, the presently preferred salt is mercuric acetate. Also, as indicated previously, the compounds may be prepared by first adding a linker arm and then the moiety A, or by adding a linker arm to which A is already attached. Thus, the chemical moiety represented by the formula . . . N may be any one of the numerous entities which ultimately result in production of the desired compounds.

Examples include

$$-CH=CH-CH_2-NH_2$$

$$-CH=CH-CH_2-O-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-NH_2,$$

$$-CH=CH-CH_2-NH\text{-biotin, and}$$

$$-CH=CH_2-CH_2-O-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-NH\text{-aminobiotin}$$

The amounts of the reactants employed in these reactions may vary widely. However, in general the amounts of unmercurated compound, mercurated compound, and palladium-containing compound will be substantially stoichiometric whereas the mercuric salt and compound . . . N will be present in molar excess, e.g. 5-20 moles of . . . N or of mercuric salt per mole of mercurated compound or unmercurated compound, respectively. In practice, amounts will vary depending upon variations in reaction conditions and the precise identity of the reactants.

Having the biotin probe directly attached to nucleotide derivatives that are capable of functioning as enzyme substrates offers considerable versatility, both in the experimental protocols that can be performed and in the detection methods (microscopic and non-microscopic) that can be utilized for analysis. For example, biotin nucleotides can be introduced into polynucleotides which are in the process of being synthesized by cells or crude cell extracts, thus making it possible to detect and/or isolate nascent (growing) polynucleotide chains. Such a procedure is impossible to do by any direct chemical modification method. Furthermore, enzymes can be used as reagents for introducing probes such as biotin into highly selective or site-specific locations in polynucleotides; the chemical synthesis of similar probe-modified products would be extremely difficult to achieve at best.

The synthesis of nucleotides containing biotin or iminobiotin was achieved as detailed in the examples set forth hereinafter. Pyrimidine nucleoside triphosphates containing either of these probes attached to the C-5 carbon atom were good to excellent substrates for a wide variety of purified nucleic acid polymerases of both prokaryotic and eukaryotic origin. These include DNA polymerase I of *E. coli*, bacteriophage T4 DNA polymerase, DNA polymerases α and β from murine (A-9) and human (HeLa) cells, and the DNA polymerase of Herpes simplex virus. Confirming data were obtained with *E. coli* DNA polymerase I using either the nicktranslation condition of Rigby, et al. (P. W. J. Rigby, M. Dieckmann, C. Rhodes and P. Berg, J. Mol. Biol. 113, 237, 1977) or the gap-filling reaction described by Bourguignon et al. (G. J. Bourguignon, P. J. Tattersall and D. C. Ward, J. Virol. 20, 290, 1976). Bio-dUTP has also been found to function as a polymerase substrate both in CHO cells, permeabilized by treatment with lysolecithin according to the method of Miller, et al. (M. R. Miller, J. C. Casteliot, Jr and A. B. Pardee, Exp. Cell Res. 120, 421, 1979) and in a nuclear replication system prepared from Herpes simplex infected BHK cells. Although biotinyl ribonucleoside triphosphates were found to function as substrates for the RNA polymerases of *E. coli* and bacteriophage T7, they are not utilized as efficiently as their deoxyribonucleotide triphosphate counterparts. Indeed, they are incorporated poorly, if at all, by the eukaryotic RNA polymerases examined (HeLa cell RNA polymerase III, calf thymus RNA polymerase II and mouse cell RNA polymerase II). While this limited range of substrate function does restrict the utility in some in vivo or in vitro transcription studies, biotinlabeled RNA probes can be prepared enzymatically from DNA templates using *E. coli* or T7 RNA polymerases or by 3' endlabeling methods using RNA ligase with compounds such as biotinyl-pCp. The AA- and NAGE-derivatives of UTP are, however, substrates for the eukaryotic RNA polymerases mentioned above. With the availability of antibodies to these analogs, the isolation of nascent transcripts by immunological or affinity procedures should be feasible.

The enzymatic polymerization of nucleotides containing biotin or iminobiotin substituents was not monitored directly, since neither of these probes were radiolabeled. However, two lines of experimental evidence clearly show that the biotinyl-nucleotides were incorporated. The first is that polynucleotides synthesized in the presence of biotinnucleotides are selectively retained when chromatographed over avidin or streptavidin affinity columns. (Tables I and II) For example, whereas normal DNA, nick translated with ^{32}P-dAMP, is quantitatively eluted upon the addition of 0.5M NaCl,

the vast majority of biotinyl-DNA or iminobiotinylDNA remains bound to the resin even after extensive washing with high salt, urea, guanidine-HCl, formamide or 50 mM NaOH. The small fraction of the radiolabel eluted by these washing conditions is not retained when applied to the resin a second time, suggesting that radioactivity is associated with DNA fragments which are free of biotin substitution. The second line of evidence is that only biotin-labeled polynucleotides are immunoprecipitated when treated with purified anti-biotin IgG followed by formalin-fixed *Staphylococcus aureus*. (Table III) It is-clear from the data in these tables that extremely small amounts of biotin can be detected by this method. These results also show that the biotin molecule can be recognized by avidin, streptavidin or specific antibodies while the DNA is still in its native, double-stranded form, a condition that is absolutely essential if the antibody-binding or avidin-affinity approaches are to be useful in probe detection employing hybridization techniques.

TABLE I

SELECTIVE RETENTION OF BIOTINIZED DNA ON AVIDIN-SEPHAROSE

Eluent		% DNA Retained on Resin Bio-DNA (1%)	T-DNA
Load -	3 × 105 cpm 10 mM Tris 7.5 + 0.2M NaCl	100	100%
(1)	0.5M NaCl	100	0.1
(2)	1.0M NaCl	99.7	<0.01
(3)	8M Urea	100	<0.01
(4)	6M guanidine-HCl	95.2	<0.01
(5)	99% formamide	94.7	<0.01
(6)	2 mM Biotin	87.6	<0.01
(7)	50 mM NaOH	89.5	<0.01

TABLE II

Affinity Chromatography of Iminobiotin-dUTP and Iminobiotinized - DNA on Streptavidin-Sepharose

Eluent		% Retained on SA-Sepharose T-DNA	^{3}H-IB-dUTP	IB-DNA
Load -	10 mM Tris HCl, 8.3 50 mM NaCl	8.7	100	99.7
(1)	0.1M NaCl	<0.1	100	99.7
(2)	1.0M NaCl	<0.01	100	99.4
(3)	8M Urea	<0.01	97.5	98.5
(4)	6M guanidine-HCl	<0.01	97.0	97.0
(5)	50 mM NH_4-acetate, pH 4.0	<0.01	<0.01	96.5
(6)	50 mM NH_4-acetate, pH 4.0 2 mM biotin	<0.01	<0.01	<0.01

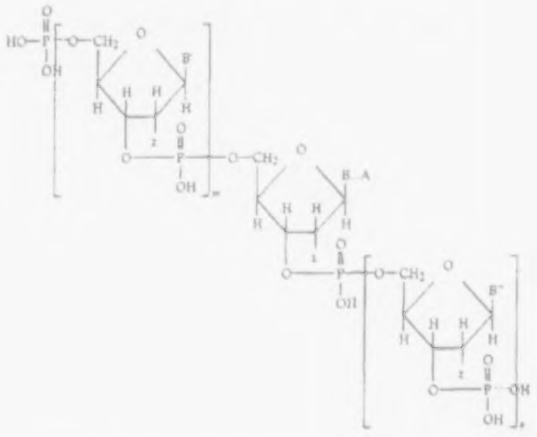
TABLE III

SELECTIVE IMMUNOPRECIPITATION OF BIO-DNA WITH ANTI-BIOTIN IgG and *STAPH AUREUS*

DNA*	Antibody	CPM in Immuno ppt.	CPM in Supernatant
T-DNA	–	70	4867
T-DNA	Anti-Bio IgG	87	5197
T-DNA	Non-immune IgG	55	5107
Bio-DNA	–	53	3836
Bio-DNA	Anti-Bio IgG	3347	736
Bio-DNA	Non-immune IgG	60	3900

*N.T. pBR-322 DNA, ^{32}P-labeled, 1% Biotin substitution.
Specific activity 2 × 10^7 cpm/μg.
Biotin detection 0.001-0.01 picoles.

Thus, it is possible to prepare novel compounds having the structure:



wherein each of B, B', and B'' represents a purine, deazapurine, or pyrimidine moiety covalently bonded to the C^1'-position of the sugar moiety, provided that whenever B, B', or B'' is purine or 7-deazapurine, it is attached at the N^9-position of the purine or deazapurine, and whenever B, B', or B'' is pyrimidine, it is attached at the N^1-position,

wherein A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded duplex formed with a complementary ribonucleic or deoxyribonucleic acid molecule.

wherein the dotted line represents a linkage group joining B and A, provided that if B is purine, the linkage is attached to the 8-position of the purine, if B is 7-deazapurine, the linkage is attached to the 7-position of the deazapurine, and if B is pyrimidine, the linkage is attached to the 5-position of the pyrimidine;

wherein z represents H— or HO —; and

wherein m and n represent integers from 0 up to about 100,000.

Of course, it should be readily understood that in general m and n will not simultaneously be 0 since, in that event, the compound becomes merely a modified nucleotide as described previously. In general B' and B" will vary within the same oligo- or polynucleotide, being alternatively uracil, cytosine, thymine, guanine, adenine, or the like. Also, in general, the variation will correspond to the ordered sequence of nucleotides which codes for the synthesis of peptides according to the well known Genetic Code. However, it is intended that the structure shown also embrace polynucleotides such as poly C, poly U, poly r(A-U), and poly d(A-U) as well as calf thymus DNA, ribosomal RNA of *E. coli* or yeast, bacteriophage RNA and DNA (R17, fd), animal viruses (SV40 DNA), chromosomal DNA, and the like, provided only that the polynucleotides be modified in accordance with this invention.

It is also to be understood that the structure embraces more than one modified nucleotide present in the oligomer or polymer, for example, from two to thirty modified nucleotides. The critical factor in this regard is that the number of modifications not be so great that the polynucleotide is rendered ineffective for the intended use.

Finally, it should be understood that modified oligo- and polynucleotides can be joined to form larger entities having the same structure so long as terminal groups are rendered compatible or reactive. These compounds can be made by enzymatic polymerization of appropriate nucleotides, especially nucleotide triphosphates in the presence of a nucleic acid template which directs synthesis under suitable conditions. Such conditions can vary widely depending upon the enzyme employed, amounts of nucleotides present, and other variables. Illustrative enzymes include DNA polymerase I of *E. coli*, bacteriophage T4 DNA polymerase, DNA polymerases α and β from murine and human (HeLa) cells, DNA polymerase from Herpes simplex virus, RNA polymerase of *E. coli*, RNA polymerase of bacteriophage T7, eukaryotic RNA polymerase including HeLa cell RNA polymerase III, calf thymus RNA polymerase II, and mouse cell RNA polymerase II.

Also, the compounds can be prepared by terminal addition to oligo- or polynucleotides to produce compounds in which m or n is 0 depending upon whether the addition is at the 5' or 3' position. Moreover, the compounds such as pCp or pUp in which the base is biotinized can be added to existing molecules employing the enzyme RNA ligase.

Modified oligo- and polynucleotides can also be prepared by chemical modification of existing oligo- or polynucleotides using the approach described previously for modification of individual nucleotides.

The various modified nucleotides, oligonucleotides, and polynucleotides of this invention may be detected by contacting the compounds with polypeptides which are capable of forming complexes therewith under suitable conditions so as to form the complexes, provided that the polypeptides include one or more moieties which can be detected when the complex or complexes is or are formed, generally by means of conventional detection techniques.

One polypeptide detector for the biotinyl-type probe is avidin. The avidin-biotin interaction exhibits one of the tightest non-covalent binding constants ($K_{diss}=10^{-15}$) seen in nature. If avidin is coupled to potentially demonstrable indicator molecules, e.g., fluorescent dyes (fluoroscein, rhodamine), electron-dense reagents (ferritin, hemocyanin, colloidal gold), or enzymes capable of depositing insoluble reaction products (peroxidase, alkaline phosphatase) the presence, location and/or quantity of the biotin probe can be established.

Avidin has, unfortunately, one property that makes it less desirable as a biotin-indicator protein when used in conjunction with nucleic acids or chromatin material. It has been reported (M. H. Heggeness, Stain Technol., 52, 165, 1977; M. H. Heggeness and J. F. Ash, J. Cell. Biol., 73, 783, 1977; E. A. Bayer and M. Wilchek, Methods of Biochemical Analysis 26, 1, 1980) that avidin binds tightly to condensed chromatin or to subcellular fractions that contain large amounts of nucleic acid in a manner which is independent of its biotin-binding property. Since avidin is a basic glycoprotein with a pI of 10.5, its histone-like character or its carbohydrate moieties are most likely responsible for these observed non-specific interactions.

A preferred probe for biotin-containing nucleotides and derivatives is streptavidin, an avidin-like protein synthesized by the soil organism *Streptomyces avidinii*. Its preparation and purification is described in Hoffman, et al., Proc. Natl. Acad. Sci., 77, 4666 (1980). Streptavidin has a much lower pI (5.0), is non-glycosylated, and shows much lower non-specific binding to DNA than avidin, and therefore offers potential advantages in applications involving nucleic acid detection methodology.

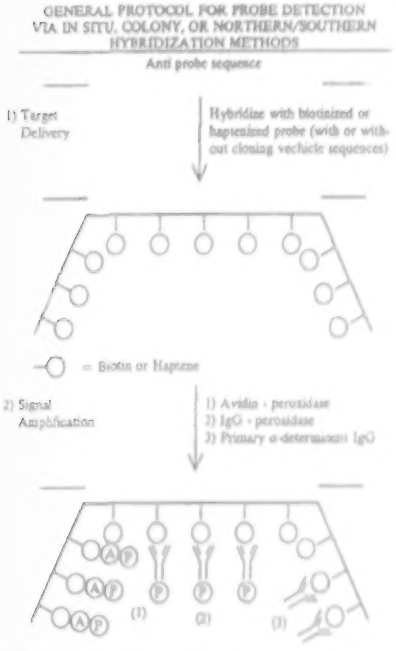
A most preferred protein for biotin-like probe detection is monospecific rabbit IgG, antibiotin immunoglobulin. This compound was prepared by immunizing rabbits with bovine serum albumin conjugated biotin as described previously (M. Berger, Methods in Enzymology, 62, 319 [1979]) and purified by affinity chromatography. Although the association constant of immunoglobulin-haptens have values of K_{assn} (10^6 to 10^{10}) which are considerably lower than for avidin-biotin complexes, they are substantially equivalent to those observed with the avidin-iminobiotin complex. Furthermore, the anti-biotin antibodies have proven extremely useful in detecting specific polynucleotide sequences on chromosomes by in situ hybridization since little, if any, non-specific binding of the antibody to chromatin material occurs.

The modified polynucleotides of this invention are capable of denaturation and renaturation under conditions compatible with their use as hybridization probes. An analysis of the thermal denaturation profiles and hybridization properties of several biotin-substituted DNA and RNA polymers clearly indicates this. For example, pBR 322 DNA or λ DNA, nick translated to introduce approximately 10–100 biotin residues per kilobase, have Tm values essentially identical to that of the control, biotin-free DNAs. Furthermore, ^{32}P-labeled, biotin-substituted, pBR 322 DNA, exhibited the same degree of specificity and autoradiographic signal intensity as control, thymidine-containing DNA, when

used as a hybridization probe for detecting bacterial colonies containing the plasmid.

In DNA duplexes, such as MVM RF DNA, in which every thymidine residue in one strand (1250 in toto per 5 Kb) is replaced by a biotinyl-nucleotide, the Tm is only 5° C. less than that of the unsubstituted control. Although the Tm of poly d(A-bioU) in which each base pair contains a bio-dUMP residue is 15° C. lower than the poly d(A-T) control, the degree of cooperativity and the extent of hyperchromicity observed both during denaturation and renaturation were the same for the two polymers. A parallel analysis of RNA duplexes and DNA/RNA hybrids indicates that their Tm's also decrease as the biotin-content of the polymer increases. However, it is clear that a substantial number of biotin-molecules can be introduced without significantly altering the hybridization characteristics of the polymers.

These results strongly suggested that biotin-substituted polynucleotides could be used as probes for detecting and/or localizing specific polynucleotide sequences in chromosomes, fixed cells, or tissue sections. The general protocol for detecting the biotin-substituted probe is schematically illustrated as follows:



This general scheme illustrates only procedures used for gene mapping (cytogenetics), and recombinant DNA-technologies. However, it can be equally well applied to the detection of nucleic acid sequences of bacterial, viral, fungal or parasite origin in clinical samples and this forms the basis of a powerful new approach to clinical diagnostics which does not rely on the use of radioisotopes.

Immunological and histochemical methods for the detection of biotin have shown that the basic approach is useable for a rapid method of gene mapping in situ hybridization and non-radioactive procedures for detecting specific nucleic acid sequences by blotting hybridization methods. Use may be made of this technology in development of new clinical diagnostic procedures.

Using this approach, it is possible to determine the presence of a specific deoxyribonucleic or ribonucleic acid molecule, particularly such a molecule derived from a living organism, e.g. bacteria, fungus, virus, yeast, or mammal. This in turn permits diagnosis of nucleic acid-containing etiological agents in a patient or other subject.

Moreover, it provides a method for screening bacteria to determine antibiotic resistance. Thus, for example, penicillin resistance in *Streptococcus pyogenes* or *Neisseria meningitidis*; tetracycline resistance in *Staphylococcus aureus, Candida albicans, Pseudomonas aeruginosa, Streptococcus pyogenes*, or *Neisseria gonorrhoeae*; and aminoglycoside resistance in *Mycobacterium tuberculosis* can be determined.

In these methods a polynucleotide is prepared which is complementary to the nucleic acid sequence which characterizes the organism or its antibiotic resistance and which additionally includes one or more modified nucleotides according to this invention. This polynucleotide is hybridized with nucleic acid obtained from the organism under scrutiny. Failure to hybridize indicates absence of the organism or of the resistance characteristic. Hybridized nucleic acid duplexes are then identified by forming a complex between the duplex and a suitable polypeptide which carries a detectable moiety, and detecting the presence of the complex using an appropriate detection technique. Positive detection indicates that the complex, the duplex and therefore the nucleic acid sequence of interest are present.

This approach can be extended to the diagnosis of genetic disorders, such as thalassemia and sickle cell anemia. The deoxyribonucleotide acid gene sequence whose presence or absence (in the case of thalassemia) is associated with the disorder can be detected following hybridization with a polynucleotide probe according to this invention based upon complex formation with a suitable detectable polypeptide.

The mapping of genes or their transcripts to specific loci on chromosomes has been a tedious and time-consuming occupation, involing mainly techniques of cell-fusion and somatic cell genetics. Although in situ hybridization has been employed successfully for mapping single-copy gene sequences in species that undergo chromosomes polytenization, such as Drosophila, detection of unique sequence genes in most higher eukaryotic chromosomes has been extremely difficult, if not impossible, using standard hybrization methods. The necessity for polynucleotide probes of very high specific radioactivity to facilitate autoradiographic localization of the hybridization site also results in rapid radio decomposition of the probe and a concomitant increase in the background noise of silver grain deposition. The use of hybridization probes with low to moderate specific radio activities requires exposure times of many days or weeks, even to detect multicopy sequences, such as ribosomal RNA genes or satellite DNA. Since recombinant DNA technology has made feasible the molecular cloning of virtually every single-copy sequence found in eukaryotic cells, it would be extremely beneficial to have a rapid and sensitive method

for mapping the chromosomal origin of such cloned genomic fragments.

Modified nucleotides may be used in a method of gene mapping by in situ hybridization which circumvents the use of radioisotopes. This procedure takes advantage of a thymidine analogue containing biotin that can be incorporated enzymatically into DNA probes by nick translation. After hybridization in situ the biotin molecules serve as antigens for affinity purified rabbit anti-biotin antibodies. Immunofluorescent antibody sandwiches made with fluorescein-labeled goat anti-rabbit IgG allow for rapid and specific cytogenetic localization of cloned gene sequences as green-yellow bands. This method offers four major advantages over conventional autoradiographic methods of in situ gene localization; less background noise, an increase in resolving power between bands, a decrease in the time required to determine the site of probe hybridization; and chemically stable hybridization probes. This method has been applied successfully to the localization of reiterated and unique DNA sequences in the polytene chromosome of *Drosophila melanogaster* and satellite DNA on mouse metaphase chromosomes.

Thus it has been found that polytene chromosomes could be used as a test system for establishing the efficacy of probes using the modified nucleotides according to the instant invention as detected by indirect immunofluorescence for in situ gene mapping. The probes included a variety of cloned Drosophila sequences obtained from Otto Schmidt and Dieter Söll, such as tRNA genes cloned in plasmid vectors with inserts of sizes ranging from about 5 to about 22 kilobases. Many of these clones have already been assigned to specific bands on the Drosophila chromosome map by conventional in situ hybridization methods employing radioisotopes.

DNA probes were nick translated in the presence of Bio-dUTP. Occasionally ^{3}H dATP and/or ^{3}H dCTP was included in the nick translation reaction mixture. This allowed both autoradiographic and immunofluorescent localization of a sequence on a single chromosome spread. In situ hybridization was performed as described in M. L. Pardue, and J. G. Gall, Methods in Cell Biol., 10, 1 (1975). After the final 2×SSC wash to remove unhybridized probe, the slides were rinsed with PBS (phosphate buffered saline) and incubated at 37° C. with 2.5 μg/ml Rabbit anti-biotin in PBS and 10 mg/ml BSA for 2-16 hours. This was followed by incubation of the slides with FITC labeled Goat anti-Rabbit IgG (Miles Laboratories, diluted 1:100 in PBS and 10 mg/ml BSA) for one-four hours. Evans Blue was often required as a red counterstain to set the chromosomes with fluorescent illumination.

When plasmids pBR 17D and pPW 532 containing 5 Kb and 22 Kb inserts, respectively, were hybridized by this method, it was found that the pattern of hybridization is reproducible from spread to spread and is observed unambiguously on greater than 90% of the chromosome spreads on a given slide.

The cloned transposable element pAC 104 is known to map at many sites along the Drosophila genome. Comparison of the autoradiograph and the fluorescent picture obtained by in situ hybridization of this probe illustrates a major advantage of this method, i.e., that where diffuse regions of silver grains appear on an autoradiograph, doublets or a series of bands are discernible by immunofluorescent labeling.

The other immediately obvious advantage of this method is the tremendous decrease in time required for gene assignments to be made by indirect immunofluorescence. An assignment of a DNA fragment to a specific band can be made within six hours of hybridization. This is in comparison to days or weeks required for autoradiographic exposure methods. This factor, in combination with increased resolution, makes the use of modified nucleotides detected by indirect immunofluorescence immediately preferable to more classical methods.

It has been shown that this immunological method also works with mammalian chromosomes wherein satellite DNA has been mapped to the centromeric regions of mouse metaphase chromosomes. The result provides a basic foundation for the development of a simple gene mapping procedure for single copy (unique) sequences in chromosomes from human and other mammals. Such a procedure should greatly facilitate our understanding of the genetic organization of the chromosome and make clinical cytogenetic diagnosis much more rapid and practical.

While a single-step "antibody sandwich" method in which the chromosome spread is challenged, post-hybridization, with rabbit anti-biotin IgG may succeed, this protocol may not generate sufficient fluorescence for unambiguous gene assignments. However, a much stronger fluorometric signal can be achieved by using the "haptene-antibody sandwich technique" described by Lamm, et al, (1972); Wofsy, et al., (1974). In this procedure the primary antibody, in our case monospecific, rabbit anti-biotin IgG, is chemically modified with a haptenization reagent, such as 2,4-dinitrofluorobenzene, preferably while the immunoglobulin is bound to an antigen affinity column (biotin-Sepharose TM). As many as 15-20 haptene (DNP) groups can be coupled to the primary antibody without decreasing its antigen binding affinity or specificity (Wallace and Wofsy, 1979). If the primary antibody treatment of the test sample is followed by an incubation with a fluorescently labeled anti-hapten IgG antibody, rather than a fluorescently labeled anti-IgG, a 5-7 fold increase in fluorescence signal can be achieved. Since one also has available monospecific guinea pig anti-DNP IgG, we can haptenize this secondary antibody with biotin and thus generate two anti-hapten IgG populations, DNP-labeled anti-biotin IgG and biotin-labeled anti-DNP IgG. If these can be used alternately to achieve several rounds of hapten -antibody sandwiching and then followed with fluorescently labeled protein A from *Staphylococcus aureus*, which binds specifically to IgG molecules from many mammalian species, it could result in an enormous amplification of the primary antibody signal with its concomitant utility.

The protein streptavidin from *Streptomyces avidini* is a potential alternative to anti-biotin IgG as a vehicle to specifically direct a coupled visualization system [e.g., fluorescent probes (above) or histochemical reagents (below)] to the site of the hybridized biotin-containing polynucleotide. One of streptavidin's advantages over anti-biotin IgG is that its affinity for biotin is $K_{assn} = 10^{15}$ whereas association constants for haptene-IgG interactions are 10^7 to 10^{10}. The fast reaction rate and extreme affinity mean that the time required to localize the biotinized probe will be minutes with streptavidin versus hours with immunologic reagents. Initial evaluations of a streptavidin detection system are currently in progress. Polytene chromosomes hybridized

with biotinized DNA probes will be incubated with streptavidin followed by a subsequent incubation with bovine serum albumin which has been doubly labeled with biotin and FITC (FITC, biotinyl-BSA). Since only one of the four streptavidin subunits is likely to be involved in binding at each biotinized DNA site, potentially one labeled BSA molecule can bind to each of the remaining three nonconjugated subunits of the streptavidin-biotinyl nucleotide complex. The fluorescence signal from this single streptavidin+FITC, biotinyl-BSA layer will be compared with a control using the basic "antibody sandwich method" described earlier.

If the "antibody sandwich" and streptavidin+FITC, biotinyl-BSA detection intensities are comparable, one can attempt to enhance the streptavidin+FITC, biotinyl-BSA system to single-copy copy sensitivity in a manner that parallels the multiple "haptene-antibody sandwich" approach. Since some of biotin groups on BSA will not be bound to the first layer of streptavidin, a second layer of streptavidin can be added until sufficient signal is obtained. For example, if in the second layer, only two streptavidin promoters bind to each first-layer BSA and each of these streptavidin protomers binds three FITC-biotinyl BSA molecules, then the second layer intensity will be twice as great as that from the first layer; for the third layer, with analogous binding stoichiometries, the fluorescent intensity will be 12-fold that of the first layer, so the total intensity will rapidly increase with successively added layers. There are plans to use a larger carrier protein such as thyroglobulin rather than BSA in order to maximize amounts of attached fluorescent and biotin probes. It may also be necessary to use a longer linker arm between the biotin probe and the carrier protein. A longer linker arm should sterically optimize the theoretical delivery of a biotinized fluorescent carrier molecule to each nonconjugated streptavidin subunit and maximize the number of streptavidin protomers in the subsequent layer which will bind to the biotinized fluorescent carrier. As before, appropriate controls will be done to insure that substitution of the carrier protein with fluorescent probes and biotin does not cause solubility and/or nonspecific binding problems.

The streptavidin-carrier protein delivery system has two significant advantages over the immunofluorescent approach in addition to its speed of delivery. First, only two protein components are needed to form the layers. Second, only the carrier protein needs to be modified and it is not necessary to maintain functional or even total structural integrity as long as the biotin groups are accessible to streptavidin.

An alternative to the fluorescence method for visualizing hybridized probes is to direct enzymes such as peroxidase, alkaline phosphatase of β-galactosidase to the hybridization site where enzymatic conversion of soluble substrates to insoluble colored precipitates permits light microscope visualization. The important advantage of this technique is that the histochemical methods are 10 to 100-fold more sensitive than fluorescence detection. In addition, the colored precipitates do not bleach with extensive light exposure thus avoiding one of the general disadvantages of fluorescent light microscopy. These enzymes can be coupled to the final antibody instead of fluorescent probes in the "haptene-antibody sandwich" technique using bifunctional reagents such as glutaraldehyde or in the case of peroxidase via oxidation of the peroxidase carbohydrate moieties to aldehydes and coupling of these residues with ϵ-amino groups of the desired protein. For the streptavidin-biotinized carrier protein method, an enzyme with biotinyl groups coupled to it could replace a fluorescently-biotinized carrier system. Alternately, the enzyme could be coupled via biotin to the last layer of streptavidin with amplification of streptavidin sites being built up in preceding layers using biotinized BSA or thyroglobulin. We will begin developing the necessary histochemical reagents and the appropriate substrate/insoluble product combinations for visualizing in situ hybridizations without background problems in the near future. The histochemical approaches to signal amplification should therefore be ready for trial in the summer of 1981.

Detecting and/or imaging very low levels of fluorescent light is possible using currently available image intensifiers or systems composed of lasers and photomultipliers. These methods permit the detection of light down to the level of individual photons. With suitable digital processing systems, images can be produced in which each point, i.e. each pixel, of the image is strictly proportional to the number of photons emitted by a point at the object. Using systems of this kind or flow systems in which the cells or parts of cells flow past a laser beam, one can obtain detection sensitivity increases for fluorescent material of factors between 100 and 1000 beyond that which can be detected by the eye. This increase is sufficient to detect the fluorescence of single copy genes.

In a preferred modification, analogs of dUTP and UTP that contain a biotin molecule covalently bound to the C-5 position of the pyrimidine ring through an allylamine linker arm have been synthesized. These biotinyl-nucleotides are efficient substrates for a variety of DNA and RNA polymerases in vitro. DNA containing low levels of biotin substitution (50 molecules or less/kilobase) has denaturation, reassociation and hybridization characteristics which are indistinguishable from that of unsubstituted control DNA.

Thus, this invention also provides a method of chromosomal karyotyping. In this method, modified polynucleotides are prepared which correspond to known genes and include modified nucleotides. These polynucleotides are hybridized with chromosomal deoxyribonucleic acid and the resulting duplexes contacted with appropriate polypeptides under suitable conditions to permit complex formation. The polypeptides include detectable moieties so that the location of the complexes can be determined and the location of specific genes thereby fixed.

Another embodiment of this invention involves detection of poly A-containing sequences using poly U in which some of the uracil bases have been modified to contain a probe. Yet another embodiment involves cyclic modified nucleotides in which two of x, y, and z are reacted to form the cyclic moiety

Such cyclic modified nucleotides may then be used to identify hormone receptor sites on cell surfaces which in turn can be used as a method of detecting cancer or tumor cells.

Finally, tumor cells can be diagnosed by preparing polynucleotides which are modified according to this invention and are complementary to the messenger ribonucleic acid synthesized from a deoxyribonucleic acid gene sequence associated with the production of polypeptides, such as α-fetal protein or carcinoembryonic antigen, the presence of which is diagnostic for specific tumor cells. Hybridization and detection of hybrid duplexes thus would provide a method for detecting the tumor cells.

The examples which follow are set forth to illustrate various aspects of the present invention but are not intended to limit in any way its scope as more particularly set forth in the claims.

EXAMPLE 1 and 2

Synthesis of biotinyl-UTP and biotinyl-dUTP

a) Preparation of Mercurated Nucleotides

UTP (570 mg, 1.0 mmole) or dUTP 554 mg, 1.0 mmole) was dissolved in 100 ml of 0.1M sodium acetate buffer pH 6.0, and mercuric acetate (1.59 gm, 5.0 mmoles) added. The solution was heated at 50° C. for 4 hours, then cooled on ice. Lithium chloride (392 mg, 9.0 mmoles) was added and the solution extracted six times with an equal volume of ethyl acetate to remove excess $HgCl_2$. The efficiency of the extraction process was monitored by estimating the mercuric ion concentration in the organic phase using 4,4'-bis(dimethylamino)-thiobenzophenone (A. N. Christoper, Analyst, 94, 392 (1969). The extent of nucleotide mercuration, determined spectrophotometrically following iodination of an aliquot of the aqueous solution as described by Dale et al. (R. M. K. Dale, D. C. Ward, D. C. Livingston, and E. Martin, Nucleic Acid Res. 2, 915 [1975]), was routinely between 90 and 100%. The nucleotide products in the aqueous layer, which often became cloudy during the ethyl acetate extraction, were precipitated by the addition of three volumes of icecold ethanol and collected by centrifugation. The precipitate was washed twice with cold absolute ethanol, once with ethyl ether, and then air dried. These thus prepared mercurated nucleotides were used for the synthesis of the allylamine-nucleotides without further purification.

b) Synthesis of allylamine-dUTP and allylamine-UTP

The mercurated nucleotides (of step a) were dissolved in 0.1M sodium acetate buffer at pH 5.0, and adjusted to a concentration of 20 mM (200 OD/ml at 267 nm). A fresh 2.0 M solution of allylamine acetate in aqueous acetic acid was prepared by slowly adding 1.5 ml of allylamine (13.3 mmoles) to 8.5 ml of ice-cold 4M acetic acid. Three ml (6.0 mmoles) of the neutralized allylamine stock was added to 25 ml (0.5 mmole) of nucleotide solution. One nucleotide equivalent of K_2PdCl_4, (163 mg, 0.5 mmole), dissolved in 4 ml of water, was then added to initiate the reaction. Upon addition of the palladium salt (Alfa-Ventron) the solution gradually turned black with metal (Hg and Pd) deposits appearing on the walls of the reaction vessel. After standing at room temperature for 18–24 hours, the reaction mixture was passed through a 0.45 mm membrane filter (nalgene) to remove most of the remaining metal precipitate. The yellow filtrate was diluted fivefold and applied to a 100 ml column of DEAE-Sephadex TM A-25 (Pharmacia). After washing with one column volume of 0.1M sodium acetate buffer at pH 5.0, the products were eluted using a one liter linear gradient (0.1-0.6M) of either sodium acetate at pH ~8.9, or triethylammonium bicarbonate (TEAB) at pH 7.5. The desired product was in the major UV-absorbing portion which eluted between 0.30 and 0.35M salt. Spectral analysis showed that this peak contained several products, final purification was achieved by reverse phase-HPLC chromatography on columns of Partisil-ODS2, using either 0.5M $NH_4H_2PO_4$ buffer at pH 3.3 (analytical separations), or 0.5M triethylammonium acetate at pH 4.3 (preparative separations) as eluents. The 5'-triphosphates of 5-(3-aminopropen-1-yl) uridine (the allylamine adduct to uridine) were the last portions to be eluted from the HPLC column and they were clearly resolved from three, as yet uncharacterized, contaminants. These nucleotides were characterized by proton NMR elemental analysis tAA-dUTP ($C_{12}H_{16}N_3O_{14}P_3Na_4.1H_2O$): theory C, 22.91; H, 2.88; N, 6.68; P, 14.77. Found, C, 23.10; H, 2.85; N, 6.49; P, 14.75. AA-UTP ($C_{12}H_{16}N_3O_{15}P_3Na_4.4H_2O$). Theory, C 20.61; H, 3.46; N, 6.01; P, 13.3. Found C, 20.67; H, 4.11; N, 5.39; P, 13.54] spectrally and chromatographically.

c) Biotination of AA-dUTP or AA-UTP

Biotinyl-N-hydroxysuccinimide ester (NHSB) was prepared from biotin (Sigma) as described previously (H. Heitzmann and F. M. Richards, Proc. Natl. Acad. Sci. USA. 71, 3537 [1974]). AA-dUTP-H_2O (63 mg, 0.1 mmole) or AA-UTP-$4H_2O$ (70 mg, 0.1 mmole) was dissolved in 20 ml of 0.1M sodium borate buffer at pH 8.5, and NHSB (34.1 mg, 0.1 mmole) dissolved in 2 ml of dimethyl formamide, was added. The reaction mixture was left at room temperature for four hours and then loaded directly onto a 30 ml column of DEAE-Sephadex TM A-25, preequilibrated with 0.1M TEAB at pH 7.5. The column was eluted with a 400 ml linear gradient (0.1-0.9M) of TEAB. Fractions containing biotinyl-dUTP or biotinyl-UTP, which eluted between 0.55 and 0.65M TEAB, were desalted by rotary evaporation in the presense of methanol and redissolved in water. Occasionally a slightly cloudy solution was obtained: this turbidity, due to a contaminant in some TEAB solutions, was removed by filtration through a 0.45 mm filter. For long term storage, the nucleotides were converted to the sodium salt by briefly stirring the solution in the presence of Dowex TM 50 (Na^+ form). After filtration the nucleotide was precipitated by the addition of three volumes of cold ethanol, washed with ethyl ether, dried in vacuo over sodium hydroxide pellets, and stored in a dessicator at −20° C. For immediate use, the nucleotide solution was made 20 mM in Tris-HCl at pH 7.5, and adjusted to a final nucleotide concentration of 5 mM. Stock solutions were stored frozen at −20° C.

Elemental analysis of the bio-dUTP and bio-UTP products yielded the following results, Bio-dUTP ($C_{22}H_{30}N_5O_{18}P_3S_1Na_6.1H_2O$). Theoretical; C, 29.80; H, 3.38; N, 7.89; P, 10.47; S, 3.61. Found, C, 30.14 H, 3.22; N, 7.63; P, 10.31; S, 3.70. Bio-UTP ($C_{22}H_{30}N_5O_{19}P_3S_1Na_4.3H_2O$): Theoretical; C, 29.15; H, 3.19; N, 7.45; P, 9.89; S, 3.41. Found; C, 28.76; H, 3.35; N, 7.68; P, 9.81; S, 3.32.

The spectral properties of bio-dUTP and bio-UTP at pH 7.5 [λ max, 289 nm (ε = 7,100); λ max, 240 nm (ε = 10,700); λ min, 262 nm (ε = 4,300)] reflect the presence of an exocyclic double-bond in conjugation with the pyrimidine ring. These nucleotides also give a strong positive reaction (an orange-red color) when treated with p-dimethylaminocinnamaldehyde in ethanolic sulfuric acid, a procedure used for biotin quantita-

tion (D. B. McCormick and J. A. Roth, Anal Biochem., 34,326, 1970). However, they no longer react with ninhydrin, a characteristic reaction of the AA-dUTP and AA-UTP starting materials.

EXAMPLES 3 and 4

Synthesis of biotinyl-CTP and biotinyl-dCTP

CTP and dCTP were a) mercurated, b) reacted with allylamine, and c) biotinized with NHS-biotin, essentially as described in Example 1. CTP (56.3 mg, 0.1 mmole) or dCTP (59.1 mg, 0.1 mmole) were dissolved in 20 ml of 0.1M sodium acetate buffer at pH 5.0, and mercuric acetate (0.159 gm, 0.5 mmoles) added. The solution was heated at 50° C. for 4.5 hours then cooled on ice. Lithium chloride (39.2 mg, 0.9 mmoles) was added and the solution extracted 6 times with ethyl acetate. The nucleotide products in the aqueous layer were precipitated by the addition of three volumes of cold ethanol and the precipitate collected by centrifugation. The precipitate was washed with absolute ethanol, ethyl ether, and then air dried. These products were used without further purification for the synthesis of AA-CTP and AA-dCTP, respectively. The mercurated nucleotides were dissolved in 0.1M sodium acetate buffer at pH 5.0 and adjusted to a concentration of 10 mM (92 OD/ml at 275 nm). 0.6 ml (1.2 mmole) of a 2.0M allylamine acetate stock (prepared as described in Example 1) was added to 10 ml of nucleotide solution (0.1 mmole) followed by the addition of K_2PdCl_4 (32.6 mg, 0.1 mmole), dissolved in 1.0 ml of H_2O. After standing at room temperature for 24 hours, the solution was filtered through a 0.45 mM membrane to remove metal precipates. The filtrate was diluted fivefold and loaded onto a 50 ml-column of DEAE-sephadex A-25, preequilibrated with 50 mM TEAB at pH 7.5. The nucleotide products were fractionated by application of a 500 ml linear gradient (0.05–0.6M) of TEAB at pH 7.5. The desired product was in the major UV absorbing portion which eluted between 0.28 and 0.38M salt. The pooled samples were desalted by rotary evaporation, dissolved in 0.5M triethylammonium acetate at pH 4.2, and final purification achieved by HPLC chromatography on columns of Partisil ODS-2, using 0.5M triethylammonium acetate as the eluent. Appropriate fractions were pooled, lyophilized, and the products dissolved in H_2O. The nucleotides were converted to the Na^+ salt by stirring briefly in the presence of Dowex TM 50 (Na^+ form). After filtration, to remove the Dowex resin, the nucleotides were precipitated by the addition of 3 volumes of cold ethanol. The precipitate was washed with ether and then air dried. Analytical results: AA-dCTP ($C_{12}H_{17}N_4O_{13}P_3Na_4.2H_2O$): Theory, C, 22.29; H, 2.63; N, 8.67; P, 14.40. Found C, 22.16; H, 2.89; N, 8.77; P, 14.18. AA-CTP ($C_{12}H_{17}N_4O_{14}Na_4.2H_2O$): Theory C, 21.75; H, 2.57; N, 8.46; P, 14.01. Found, C, 22.03; H, 2.47; N, 8.69; P, 13.81; Spectral properties in 0.1M Borate buffer at PH 8.0, λ max 301 nm (ε=6,400), λ min 271 nm (ε=3,950) λ max 250 nm (ε=9,700). Both AA-dCTP and AA-CTP give a positive ninhydrin test. AA-CTP (6.6 mg, 0.01 mmole) or AA-dCTP (6.4 mg, 0.01 mmole) was dissolved in 5 ml of 0.1M sodium borate buffer at pH 8.5, and NHS-biotin (3.4 mg, 0.01 mmole), dissolved in 0.2 ml of dimethylformamide, was added. After sitting at room temperature for 4 hours the sample was chromatographed on a 10 ml column of DEAE-Sephadex A-25, using a 150 ml linear gradient (0.1–0.9M) of TEAB at pH 7.5, as eluent. Fractions containing biotinyl-CTP or biotinyl-dCTP, which eluted between 0.50 and 0.60M TEAB, were pooled, desalted by rotary evaporation, and after being adjusted to a final concentration of 5 mM in 0.0M Tris-HCl buffer at pH 7.5, were frozen at −20° C. The products give a strong positive reaction for biotin with p-dimethylaminocinnamldehyde in ethanolic sulfuric acid but give a negative test for primary amines when sprayed with ninhydrin. Further structural characterization of these products is in progress.

EXAMPLES 5 and 6

Synthesis of Iminobiotinyl-UTP and Iminobiotinyl-dUTP

Iminobiotin hydrobromide was prepared from biotin as described previously (K. Hofmann, D. B. Melville and V. du Vigneaud, J. Biol. Chem., 141, 207–211, 1941; K. Hofmann and A. E. Axelrod, Ibid., 187., 29–33, 1950). The N-hydroxysuccinimide (NHS) ester of iminobiotin was prepared using the protocol previously described for the synthesis of NHS-Biotin (H. Heitzmann and F. M. Richards, Proc. Nat. Acad. Sci. USA, 71, 5537, 1974). AA-UTP (7.0 mg, 0.01 mmole) or AA-dUTP (6.3 mg, 0.01 mmole), prepared as detailed in example 1 (part b), was dissolved in 5 ml of 0.1M sodium borate buffer at pH 8.5, and NHS-iminobiotin (3.5 mg, 0.01 mmole), dissolved in 0.5 ml of dimethylformamide, was added. The reaction mixture was left at room temperature for 12 hours and then loaded directly onto a 10 ml column of DEAE-Sephadex A-25, preequilibrated with 0.05M TEAB at pH 7.5. The column was eluted with a 150 ml linear gradient (0.05–0.6M) of TEAB. Fractions containing iminobiotin-UTP or iminobiotin-dUTP, which eluted between 0.35 and 0.40M TEAB, were desalted by rotary evaporation in the presence of methanol and dissolved in H_2O. The products contained a small amount of allylamine-nucleotide adduct as an impurity, as judged by a weak positive result in the ninhydrin test. Final purification was achieved by affinity chromatography on avidinsepharose. Fractions of the impure product, made 0.1M in sodium borate buffer at pH 8.5, were applied to a 5 ml column of avidin-sepharose and washed with 25 ml of the same buffer. The column was then washed with 50 mM ammonium acetate buffer at pH 4.0, which eluted the desired iminobiotin-nucleotide product in a sharp peak. The nucleotide was precipitated by the addition of 3 volumes of cold ethanol, washed with ethylether, dried in vacuo over sodium hydroxide pellets and stored in a dessicator at −20° C. Products were characterized by elemental analysis, as well as by spectral and chromotographic properties.

EXAMPLES 7 and 8

Synthesis of NAGE-UTP and NAGE-dUTP

Allyl (3-ammo-2-hydroxy-)propyl ether, abbreviated MAGE, was prepared from allyl glycidyl ether (Age) (obtained from Aldrich Chemical Co.). 10 ml of Age (84 mmole) was added slowly (in a fume hood) to 50 ml of 9M ammonium hydroxide and the mixture allowed to stand at room temperature for six hours. Excess ammonia was removed by rotary evaporation under reduced pressure to yield a viscous yellow oil. Analysis of this product by proton NMR showed that it possessed the required structure. 5-mercuri-dUTP (0.1 mmole) or 5-mercuri-UTP (0.2 mmole) was dissolved in 2–4 ml of 0.2M sodium acetate buffer at pH 5.0, and a 16 fold

molar excess of NAGE adjusted to pH 5.0 with acetic acid prior to use, was added. The final reaction volumes (4.3 and 8.4 ml) had nucleotide concentrations of 43 and 42 mM, respectively. One equivalent of K_2PdCl_4 (0.1 or 0.2 mmoles) was added to initiate the reaction. After standing at room temperature for 18 hours, the reaction mixtures were filtered through 0.45 μmM membranes the samples diluted five-fold, and chromatographed on columns of DEAE-Sephadex A-25, using linear gradients (0.1–0.6M) of sodium acetate. Fractions containing the desired products, as judged by their UV spectra and characteristic HPLC elution profiles on Partisil ODS-2, were pooled, diluted, and further purified by re-chromatography on DEAE-Sephadex using shallow gradients (0.1-0.5M) of ammonium bicarbonate at pH 8.5. Under these conditions the majority of the NAGE-dUTP (or NAGE-UTP)could be cleanly separated from residual impurities. Proton NMR spectra were obtained at this stage of purification after the nucleotides were lyophilized and redissolved in D_2O. For elemental analysis, the products were converted to their sodium salt form. Typical analytical results: NAGE-dUTP ($C_{15}H_{22}N_3O_{16}P_3Na_4.2\ H_2O$). Theory, C, 24.99; H, 3.63; N, 5.83; P, 12.88. Found, C, 25.39; H, 3.71; N, 5.63; P, 12.88.

EXAMPLE 9

Uses of Labeled DNA Sequences

1. Karyotyping

(a) Select from a human gene library some 100 to 200 clones. Label them as described above, and for each clone locate its place or places of hybridization visually or with a low-light-level video system. For those clones which correspond to a unique sequence gene this determines the location of the cloned DNA on a particular human chromosome. Obtain several clones for each chromosome. Each of these labeled clones can be used to identify particular chromosomes. They can also be used in combination to identify each of the 46 chromosomes as being one of the 22 autosomal pairs or the X or the Y. By allowing one set of labeled clones to hybridize to the chromosomes and then adding a fluorescent stain to the label, the set of clones and their locations can be visualized and will fluoresce with a particular color. A second set of labeled clones could then be used and reacted with a second fluorescent dye. The same process can be repeated a number of times. Thus one can, if desired, have several sets of fluorescent labels attached to the cellular DNA at different but specific locations on each of the chromosomes. These labels could be used for visual or computerized automatic karyotyping.

(b) For automatic karyotyping, one could use one set of clones to identify the approximate location of each of the 46 chromosomes by finding sets of spots corresponding to the number of labeling sites on each chromosome. Thus, it is possible by computer analysis of the digitized images to determine if the chromosomes are suitably spread for further analysis. If they are suitably spread, then one can use computer analysis to identify each of the individual chromosomes by the location and distribution of the labelled spots on each one.

By using the fact that the fluorescent spots can be placed at specific locations on each chromosome, one can carry out either manual or automatic karyotyping very much more effectively than without such labels.

II. Diagnosis of Genetic Disorders

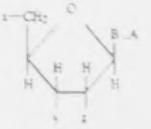
By selecting the clones which bind specifically to a particular chromosome, such as number 23, it is possible to count the number of copies of the particular chromosome in a cell even if the chromosomes are not condensed at metaphase. Thus when fetal cells are obtained for prenatal diagnosis of trisomy 21, the diagnosis can be done even if the chromosomes are not condensed at metaphase. If necessary, two sets of labels can be used—one which would be specific for chromosome 23 and one for some other chromosome. By measuring in each cell the ratio of the two labels, which might be of different colors, it is possible to identify the cells which show an abnormal number of chromosomes number 23. This procedure could be used either on slides with a low-light-level video system or in a flow cytometer system using laser excitation. It can be used to determine any abnormal chromosome number.

III. Microorganism Detection and Identification

The labeling of specific sequences of DNA as described above permits identification and counting of individual bacteria. In order to identify the individual bacteria to which a particular fragment of DNA hybridizes the sensitivity must be such that a single labelled structure can be detected. This can be done using a low-light-level video system and computer summation of images, or by using some other device for intensifying the light image. A flow system can also be used if the sensitivity can be made sufficiently grand. If one immobilized the bacteria on a slide their location could be found and the number of such fluorescent spots counted. This would provide a count of all of those bacteria which contain DNA which can hybridize with the specific clone utilized. If the clone is selected as being specific for a particular strain or bacteria, then one can count the number of organisms of that strain. In addition,any antibiotic resistance for which a particular gene has been identified could be characterized in a similar way using, as a probe, the DNA sequence which is contained in the antibiotic resistance gene. In addition,a probe could be used which is specific for a resistance plasmid containing one or more antibiotic resistance genes. In addition to individual bacteria, groups of bacterial cells of a particular strain can be detected and their number estimated if they are located in a small spot so that the total fluorescence specific to the hybridized DNA in the spot can be measured. In this way the number of organisms containing a specific DNA sequence can be measured in a mixture of bacteria.

We claim:

1. An oligo- or polynucleotide containing a nucleotide having the structure

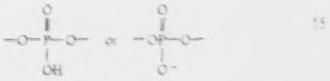


wherein B represents a 7-deazapurine or a pyrimidine moiety covalently bonded to the C1'-position of the sugar moiety, provided that whenever B is a 7-deazapurine, the sugar moiety is attached at the N9-position of the 7-deazapurine, and whenever B is a pyrimidine, the sugar moiety is attached at the N1-position of the pyrimidine,

wherein A comprises at least three carbon atoms and represents at least one component of a signaling moiety capable of producing a detectable signal.

wherein B and A are covalently attached directly or through a linkage group that does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to hybridize with a nucleic acid and does not substantially interfere with formation of the signalling moiety or detection of the detectable signal, provided also that if B is 7-deazapurine, A or the linkage group is attached to the 7-position of the deazapurine, and if B is pyrimidine, A or the linkage group is attached to the 5-position of the pyrimidine;

wherein one of x and y represents



and the other of x and y is absent or represents —OH or —H; and

wherein z represents H— or HO—.

2. An oligo- or polynucleotide of claim 1 wherein B is selected from the group consisting of uracil, cytosine, deazaadenine, and deazaguanine.

3. An oligo- or polynucleotide of claim 1 wherein A is a ligand.

4. An oligo- or polynucleotide of claim 1 wherein A is a hapten.

5. An oligo- or polynucleotide of claim 4 wherein A is biotin.

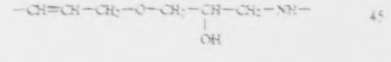
6. An oligo- or polynucleotide of claim 4 wherein A is iminobiotin.

7. An oligo- or polynucleotide of claim 1 wherein the linkage group includes an olefinic bond at the α-position relative to B.

8. An oligo- or polynucleotide of claim 1 wherein the linkage group includes the moiety —CH_2—NH—.

9. An oligo- or polynucleotide of claim 7 wherein the olefinic linkage group is the moiety —CH=CH—CH_2—NH—.

10. An oligo- or polynucleotide of claim 7 wherein the wherein the olefinic linkage group is



11. An oligo- or polynucleotide of claim 1 wherein A is an organic moiety containing at least five carbon atoms.

12. An oligo- or polynucleotide of claim 1 wherein z is HO—.

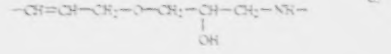
13. An oligo- or polynucleotide of claim 1 wherein z is H—.

14. An oligo- or polynucleotide of claim 11 wherein A is biotin.

15. An oligo- or polynucleotide of claim 11 wherein A is iminobiotin.

16. An oligo- or polynucleotide of claims 14 or 15 wherein the linkage group is —CH=CH—CH_2—NH—.

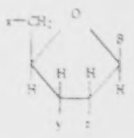
17. An oligo- or polynucleotide of claim 14 or 15 wherein the linkage group is



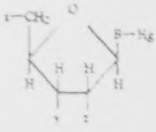
18. An oligo- or polynucleotide of claim 14 or 15 wherein B is uracil.

19. A method of making the oligo- or polynucleotide of claim 1 comprising the steps of:

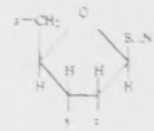
(a) reacting an oligo- or polynucleotide containing a nucleotide having the structure



with a mercuric salt in a suitable solvent under suitable conditions so as to form a mercurated derivative compound having the structure



(b) reacting said mercurated derivative compound with a chemical moiety reactive with the —Hg+ portion of said mercurated compound and represented by the formula —N, said reaction being carried out in an aqueous solvent and in the presence of a palladium-containing compound under suitable conditions so as to form a compound having the structure



wherein N is a reactive terminal functional group or is A; and

(c) when N is A, recovering said oligo- or polynucleotide of claim 1; or when N is a reactive terminal group, reacting said compound with a compound having the structure M—A wherein M represents a functional group reactive with N in an aqueous solvent under suitable conditions so as to form said oligo- or polynucleotide of claim 1 and recovering said oligo- or polynucleotide.

20. A method in accordance with claim 19 wherein said suitable conditions comprise a pH in the range from about 4 to 8, a temperature in the range from about 20° C. to 30° C., and a reaction time in the range from about 3 to 24 hours.

21. A method in accordance with claim 19 wherein said mercuric salt is mercuric acetate.

22. A method in accordance with claim 19 wherein said chemical moiety represented by the formula —N is

—CH=CH—CH_2—NH$_2$

23. A method in accordance with claim 19 wherein said chemical moiety represented by the formula ... N is

24. A method in accordance with claim 19 wherein said aqueous solvents include a buffer.

25. A method in accordance with claim 24 wherein said buffer is selected from the group consisting of sodium acetate, potassium acetate, sodium citrate, potassium citrate, potassium citrate-phosphate, tris-acetate, and borate-sodium hydroxide.

26. A method in accordance with claim 25 wherein the concentration of said buffer is less than about 2.0 molar.

27. A method in accordance with claim 19 wherein in step (b) the aqueous solvent additionally includes an organic solvent.

28. A method in accordance with claim 27 wherein said organic solvent is water-miscible.

29. A method in accordance with claim 27 wherein said organic solvent is selected from the group consisting of alcohols, ketones, and amides.

30. A method in accordance with claim 29 wherein said organic solvent is selected from the group consisting of methanol, ethanol, propanol, glycerin, dioxane, acetone, pyridine, and dimethylformamide.

31. A method in accordance with claim 29 wherein A comprises biotin or iminobiotin, and M is selected from the group consisting of N-hydroxy-succinimide ester, imidate, anhydride, isothiocyanate, and epoxide.

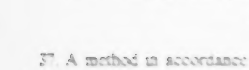
32. A method in accordance with claim 19 wherein M is an N-hydroxysuccinimide ester.

33. A method in accordance with claim 19 wherein M is selected from the group consisting of imidate, anhydride, isothiocyanate, and epoxide.

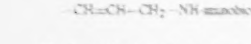
34. A method in accordance with claim 19 wherein N is selected from the group consisting of thiol, carboxylic acid, epoxide, and amine.

35. A method in accordance with claim 19 wherein said chemical moiety represented by the formula ... N is

36. A method in accordance with claim 19 wherein said chemical moiety represented by the formula ... N is



37. A method in accordance with claim 19 wherein said chemical moiety represented by the formula ... N is



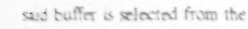
38. A method in accordance with claim 19 wherein said chemical moiety represented by the formula ... N is

39. A double-stranded polynucleotide duplex which includes the oligo- or polynucleotide of claim 1.

40. The duplex of claim 39 wherein said polynucleotide strands are ribonucleic acid molecules.

41. The duplex of claim 39 wherein said polynucleotide strands are deoxyribonucleic acid molecules.

42. An oligo- or polynucleotide sequence comprising at least one of a moiety having the structure:



wherein B represents a 7-deazapurine or a pyrimidine moiety suitable for incorporation into a polynucleotide and;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing a detectable signal;

wherein B and A are covalently attached directly or through a linkage group that does not substantially interfere with the characteristic ability of the sequence to hybridize with a nucleic acid and does not substantially interfere with formation of the signalling moiety or detection of the detectable signal, provided also that if B is 7-deazapurine, A or the linkage group is attached to the 7-position of the deazapurine, and if B is pyrimidine, A or the linkage group is attached to the 5-position of the pyrimidine.

43. An oligo- or polynucleotide sequence of claim 42 wherein A is a ligand.

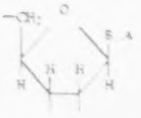
44. An oligo- or polynucleotide sequence of claim 42 wherein A is a polypeptide.

45. An oligo- or polynucleotide sequence wherein A is fluorescent, electron dense, or is an enzyme capable of reacting with a substrate to form a detectable reaction product.

46. An oligo- or polynucleotide sequence of claim 42 wherein A is a moiety consisting of at least five carbon atoms.

47. An oligo- or polynucleotide sequence of claim 42 wherein B is a pyrimidine.

48. An oligo- or polynucleotide containing therein a sugar moiety having the structure

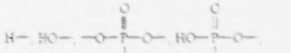


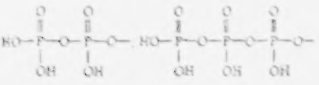
wherein B represents a 7-deazapurine or a pyrimidine moiety covalently bonded to the C^1-position of the sugar moiety, provided that whenever B is a 7-deazapurine, the sugar moiety is attached at the N^9-position of the 7-deazapurine, and whenever B is a pyrimidin, the sugar moiety is attached at the N^1-position of the pyrimidine;

wherein A comprises at least three carbon atoms and represents at least one component of a signaling moiety capable of producing a detectable signal; and

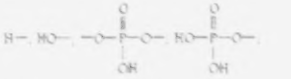
wherein B and A are covalently attached directly or through a linkage group that does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to hybridize with a nucleic acid and does not substantially interfere with formation of the signalling moiety or detection of the detectable signal, provided also that if B is 7-deazapurine, A or the linkage group is attached to the 7-position of the deazapurine, and if B is pyrimidine, A or the linkage group is attached to the 5-position of the pyrimidine.

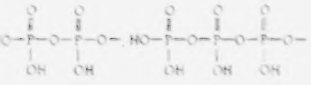
49. An oligo- or polynucleotide of claim 48, wherein the sugar moiety has attached to its C^3-position a member selected from the group consisting of





50. An oligo- or polynucleotide of claim 48, wherein the sugar moiety has attached to its C^5-position a member selected from the group consisting of





51. An oligo- or polynucleotide of claim 48, wherein the sugar moiety has attached to its C^2-position a H— or HO— group.

52. A method in accordance with claim 19, wherein the palladium-containing compound is K_2PdCl_4.

53. An oligo- or polynucleotide of claim 48 wherein A is a ligand.

54. An oligo- or polynucleotide of claim 3 or 53 wherein the ligand is selected from the group consisting of a hapten, an antigen, a cofactor, biotin and iminobiotin.

55. An oligo- or polynucleotide of claim 3 or 53 wherein the ligand is selected from the group consisting of dinitrophenol, lipoic acid and an olefinic compound.

56. An oligo- or polynucleotide of claim 3 or 53 wherein the ligand is capable of forming a complex by binding with a detectable polypeptide.

57. An oligo- or polynucleotide of claim 56 wherein the detectable polypeptide is selected from the group consisting of an antibody, an enzyme, streptavidin and avidin.

58. An oligo- or polynucleotide of claim 56 wherein an indicator molecule is associated with or bound to the detectable polypeptide.

59. An oligo- or polynucleotide of claim 58 wherein the indicator molecule is fluorescent, electron dense, or an enzyme capable of depositing insoluble reaction products.

60. An oligo- or polynucleotide of claim 59 wherein the enzyme is selected from the group consisting of alkaline phosphatase, peroxidase and β-galactosidase.

61. An oligo- or polynucleotide of claim 59 wherein the fluorescent indicator molecule is selected from the group consisting of fluorescein and rhodamine.

62. An oligo- or polynucleotide of claim 59 wherein the electron dense indicator molecule is selected from the group consisting of ferritin, hemocyanin and colloidal gold.

63. An oligo- or polynucleotide of claim 58 wherein the indicator molecule is covalently linked to the detectable polypeptide.

64. An oligo- or polynucleotide of claim 58 wherein the detectable polypeptide is indirectly detectable by specifically complexing the detectable polypeptide with a second polypeptide covalently linked to an indicator molecule.

65. An oligo- or polynucleotide of claim 64 wherein said detectable polypeptide is selected form the group consisting of avidin and streptavidin and the second polypeptide is selected from the group consisting of biotin and iminobiotin.

66. An oligo- or polynucleotide of claim 56 wherein at least one compound is labeled with a first indicator molecule and at least one other compound is labeled with a second indicator molecule.

67. An oligo- or polynucleotide of claim 1 or 48 wherein A comprises an indicator molecule.

68. An oligo- or polynucleotide of claim 67 wherein said indicator molecule is fluorescent, electron dense, or is an enzyme capable of depositing insoluble reaction products.

69. An oligo- or polynucleotide of claim 68 wherein the enzyme is selected from the group consisting of alkaline phosphatase, peroxidase and β-galactosidase.

70. An oligo- or polynucleotide of claim 68 wherein the fluorescent indicator molecule is selected from the group consisting of fluorescein and rhodamine.

71. An oligo- or polynucleotide of claim 68 wherein the electron dense compound is selected from the group consisting of ferritin, hemocyanin and colloidal gold.

* * * * *

APPENDIX B

SUPPLEMENTAL AMENDMENT OF MARCH 21, 1986, U.S. PATENT APPLICATION SERIAL NO. 496,915

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Ethel G. Love
Group	:	123
Applicants	:	David C. Ward et al.
Serial No.	:	496,915
Filed	:	May 23, 1983
For	:	MODIFIED NUCLEOTIDES AND METHODS OF PREPARING AND USING SAME

New York, New York
March 21, 1986

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SUPPLEMENTAL AMENDMENT

Sir:

Kindly amend the above-identified application as follows:

IN THE CLAIMS

Please amend claims 145, 149, 150, 155, 163, 164, 166, 172, 173, 183, 191, 192 and 199.

145. (four times amended) A nucleotide or oligo- or polynucleotide sequence comprising at least one of a moiety having the structure:

-BA

wherein B represents a 7-deazapurine or a pyrimidine moiety;

wherein A [comprises] represents a moiety selected from the group consisting of biotin and iminobiotin;

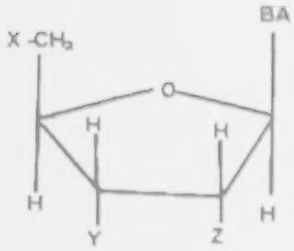
provided that if B is a 7-deazapurine, A is attached to the 7-position of the deazapurine, and if B is a pyrimidine, A is attached to the 5-position of the pyrimidine, A being attached to B directly or through a linkage group said linkage group not interfering substantially with the characteristic ability of A to form a stable complex with avidin.

149. (four times amended) [A] The nucleotide or oligo- or polynucleotide sequence according to [claim] Claim 145, wherein [said A also comprises a second moiety selected from the group consisting of a moiety including] said linkage group is characterized by at least one of an olefinic bond at the α-position relative to B and a [moiety including] $-CH_2NH-$ [, the second moiety linking B to the biotin or iminobiotin].

150. (twice amended) The nucleotide or oligo- or polynucleotide sequence in accordance with Claim 149, wherein the linkage group is characterized by [second moiety includes] the moiety $-CH=CH-CH_2-NH-$ or

$$-CH=CH-CH_2-O-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-NH-$$

155. (four times amended) A compound having the structure:

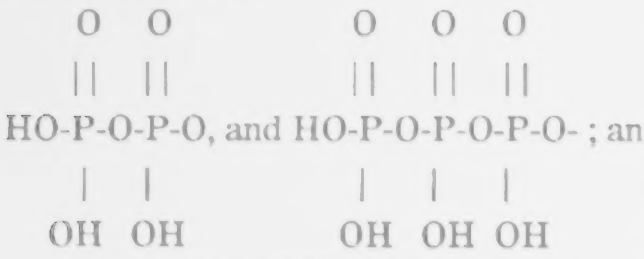


wherein B represents a 7-deazapurine or a pyrimidine moiety covalently bonded to the $C^{1'}$- position of the sugar moiety, provided that when B is a 7-deazapurine, it is attached to the N^9-position of the deazapurine, and when B is a pyrimidine, it is attached at the N^1-position of the pyrimidine;

wherein A [comprises] represents a moiety selected from the group consisting of biotin and iminobiotin;

provided that if B is a 7-deazapurine, A is attached to the 7-position of the deazapurine, and if B is a pyrimidine, A is attached to the 5-position of the pyrimidine, A being attached to B directly or through a linkage group, said linkage group not interfering substantially with the characteristic ability of A to form a stable complex with avidin;

wherein X represents a moiety selected from the group consisting of:



; and

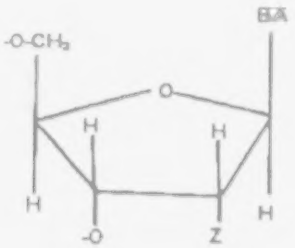
wherein Y is -OH and Z is -OH or -H.

163. (three times amended) The compound [is] in accordance with Claim 155, wherein [said A also comprises a second moiety selected from the group consisting of a moiety including] said linkage group is characterized by at least one of an olefinic bond at the α-position relative to B and a [moiety including] $-CH_2NH-$ [, the second moiety linking B to the biotin or iminobiotin].

164. (twice amended) The compound in accordance with Claim 163, wherein the linkage group is characterized by [second moiety includes] a moiety selected from the group consisting of $-CH=CH-CH_2-NH-$ and

$$-CH=CH-CH_2-O-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-NH-$$

166. (four times amended) A poly- or oligonucleotide sequence which comprises at least one of a first moiety having the structure:

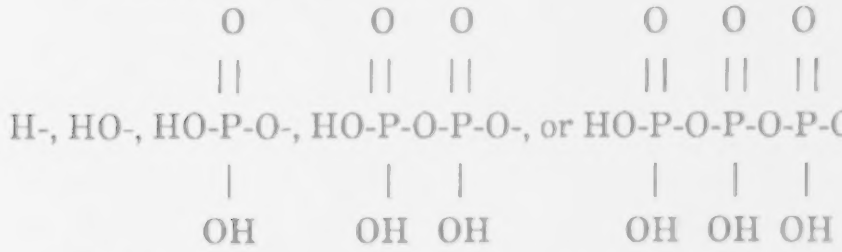


wherein B represents a purine, a 7-deazapurine or a pyrimidine moiety covalently bonded to the $C^{1'}$-position of the sugar moiety, provided that when B is a purine or a 7-deazapurine, it is attached to the N^9-position of the purine or deazapurine, and when B is a pyrimidine, it is attached at the N^1-position of the pyrimidine;

wherein A [comprises] represents a moiety selected from the group consisting of biotin and iminobiotin;

provided that if B is a purine, A is attached to the 8-position of the purine, if B is a 7-deazapurine, A is attached to the 7-position of the deazapurine, and if B is a pyrimidine, A is attached to the 5-position of the pyrimidine, A being attached to B directly or through a linkage group, said linkage group not interfering substantially with the characteristic ability of A to form a stable complex with avidin; and

wherein Z represents:

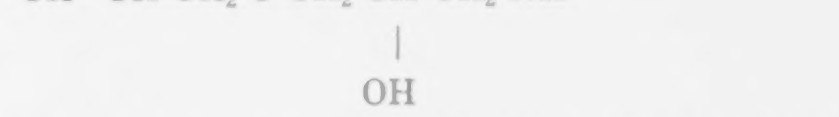


H-, HO-, HO-P-O-, HO-P-O-P-O-, or HO-P-O-P-O-P-O-

OH OH OH OH OH OH OH

172. (three times amended) The sequence in accordance with Claim 166, wherein [said A also comprises a second moiety selected from the group consisting of a moiety including] said linkage group is characterized by at least one of an olefinic bond at the α-position relative to B and a [moiety including] $-CH_2-NH-$[, the second moiety linking B to the biotin or iminobiotin].

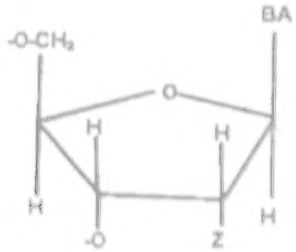
173.(twice amended) The sequence in accordance with Claim 172, wherein the linkage group is characterized by [second moiety includes the] a moiety selected from the group consisting of $-CH=CH-CH_2-NH-$ and



OH

183. (four times amended) A double-stranded RNA or DNA duplex or DNA-RNA hybrid which comprises:

(i) in one strand a poly- or oligonucleotide sequence which comprises at least one of a moiety having the structure:

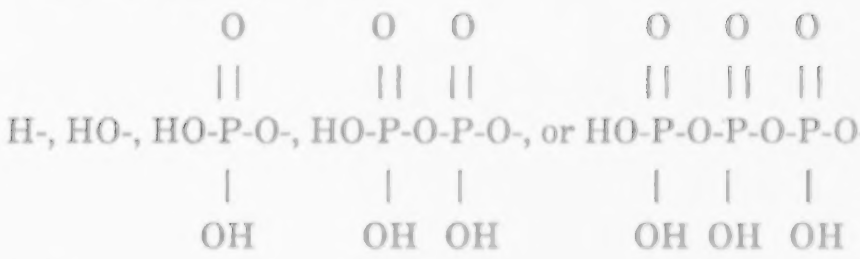


wherein B represents a purine, a 7-deazapurine or a pyrimidine moiety covalently bonded to the $C^{1'}$-position of the sugar moiety, provided that when B is a purine or a 7-deazapurine, it is attached at the N^9-position of the purine or deazapurine, and when B is a pyrimidine, it is attached at the N^1-positon of the pyrimidine;

wherein A represents [comprises] a moiety selected from the group consisting of biotin and iminobiotin;

provided that if B is a purine, A is attached to the 8-position of the purine, if B is a 7-deazapurine, A is attached to the 7-position of the deazapurine, and if B is a pyrimidine, A is attached to the 5-position of the pyrimidine, A being attached to B directly or through a linkage group, said linkage group not interfering substantially with the characteristic ability of A to form a stable complex with avidin; and

wherein Z represents



and

(ii) in the second strand, a poly- or oligonucleotide sequence containing neither a biotin or iminobiotin.

191. (three times amended) The duplex or hybrid in accordance with Claim 183, wherein [said A also comprises a second moiety selected from the group consisting of a moiety including] said linkage group is characterized by at least one of an olefinic bond at the α-position relative to B and a [moiety including] $-CH_2-NH-$.

192. (twice amended) The duplex or hybrid in accordance with Claim 191, wherein the linkage group is characterized by [second moiety includes] a moiety selected from the group consisting of $-CH=CH-CH_2-NH-$ and

199. (twice amended) A nucleotide or oligo- or polynucleotide sequence comprising at least one of a moiety having the structure:

-BA

wherein B represents purine;

wherein A [comprises] represents a [first] moiety selected from the group consisting of biotin and iminobiotin, attached to the 8-position of the purine, A being

attached to B through a linkage group, said linkage group not interfering substantially with the characteristic ability of A to form a stable complex with avidin [comprising] an olefinic bond at the α-position relative to B[, the second moiety linking B to the biotin or iminobiotin].

REMARKS

Applicants express their appreciation for the courtesy extended to their attorneys, James F. Haley, Jr., and Samuel B. Abrams, during a February 5, 1986 interview with Examiner Love. Applicants make that interview of record here.

At the interview the Examiner's rejections of Claims 145, 148-150, 155, 162-164, 166, 171-174, 177, 183, 184, 189-192 and 199 under 35 U.S.C. §112, paragraphs one and two, and applicants' February 3, 1986 Amendment in response were discussed.

With respect to the Examiner's contention (1) that the term "a compound" in Claims 145, 149 and 199 was "so broad that the scope of the claimed compound is indeterminable", applicants' attorneys pointed out that Claims 145, 149 and 199 as amended on February 3 avoided the objected to language. In view of those amendments, applicants' attorneys understood that the Examiner no longer maintained her rejection of Claims 145, 149, and 199, except to the extent referred below.

With respect to the Examiner's contention (2) that the definition of a linkage group "..." was absent from the claims, making their scope "indeterminable," applicants' attorneys pointed to their February 3 amendment of Claims 145, 149, 150, 155, 163, 164, 166, 172, 173, 183, 191, 192 and 199 omitting the objected to "..." terminology. Applicant' attorneys also stated that the amended claims

with their "comprising" and "including" terminology defined the invention by specific label -- biotin or iminobiotin -- and by specific position of attachment of that label to the base that characterizes the nucleotides and the oligo- and polynucleotides of the invention. Furthermore, they urged that the linkage group attaching the label to the base was optional and irrelevant to the invention and that substantially any linkage group could be used without departing from the scope of the disclosed invention. Applicants' attorneys also pointed out that the amended claims were no broader than the specification, that there was no art of record that anticipated those claims or made their subject matter obvious, and that the subject matter of those claims was operative and specifically exemplified in the specification. Examiner Love, although not contesting any of those facts, still considered the claims "open-ended and indefinite" because of their "comprising" and "including" terminology.

To speed the allowance of this patent application, applicants have again amended their claims to clarify the attachment of A to B. As amended, the claims avoid the "comprising" and "including" terminology objected to by Examiner Love and define the A to B attachment clearly and distinctly. The amended claims encompass nucleotides or oligo- or polynucleotide sequences in which the biotin or iminobiotin moiety (A) is attached to the base (B) either directly or through a linkage group which does not interfere substantially with the characteristic ability of A to form a stable complex with avidin. This language defines the optional linkage group in terms of a specific and unambiguous test – interference with A's characteristic ability to bind to avidin. In selecting this test to define the linkage group, applicants do not suggest that A can only bind to avidin. As described in the specifi-

cation, A can bind to a variety of polypeptides. However, for the purposes of a definition of useful linkage groups, only the binding of A to avidin need be considered.

Support for this amendment can be found in the specification, for example, on page 27, line 26-page 28, line 9 which describes the detection of the claimed compounds "by contacting the compounds with polypeptides [e.g., avidin] which are capable of forming complexes therewith under suitable conditions so as to form the complexes...." Further support is found at page 13, lines 10-31 and at page 14, lines 1-13 of the specification, where preferred linkage groups are specifically described.

The amended claims are no broader than the specification. They are also not anticipated or made obvious by any of the documents of record. And, the subject matter of the amended claims is operative and exemplified in the specification. Accordingly, applicants request that Examiner Love allow the amended claims.

With respect to the Examiner's contention (3) that claims encompassing deazapurine derivatives were "insufficiently disclosed in the specification", applicants' attorneys pointed to pages 6 and 17 of the specification and urged that the synthesis of the deazapurines was known to be analogous to that of pyrimidines. Accordingly, the specification adequately supports the claimed "deazapurines". It is applicants' attorneys' understanding that the Examiner has withdrawn her rejection of those compounds.

Finally, with respect to the Examiner's contention (4) that Claim 183 was indefinite and too broad, applicants' attorneys pointed out that the amended claims had omitted the objected to "to be discriminated" or "during

detection" language. As a result, the Examiner withdrew her rejection.

In summary, as a result of their February 3 amendments (contentions 3 and 4) and the above amendments (contentions 1 and 2), applicants have avoided and resolved all of Examiner Love's rejections under 35 U.S.C. §112. The amended claims are now in condition for allowance.

With respect to the Examiner Love's rejection of Claims 145, 148-150, 155, 162-164, 166, 171-174, 177, 183, 184, 189-192 and 192 as unpatentable under 35 U.S.C. §103, applicants' attorneys discussed at the February 5 interview the various cited documents* and argued that none taught or suggested the combination of applicants' labels and their positions of labelling nucleotides. As a result, the Examiner agreed that the "references of record are not seen to show the claimed invention," except as that invention is claimed in claims 145 and 148-150.

Applicants request Examiner Love to reconsider her rejection of Claims 145 and 148-150. The subject matter of amended claims 145, 148-150 are not taught or suggested by the art. For example, A. Sodja and N. Davidson, "Gene Mapping And Gene Enrichment By the Avidin-Biotin Interaction: Use of Cytochrome-C As A Polyamine Bridge," Nucl. Acids Res., 5, pp. 383-99 (1978)

---

* United Kingdom Patent 2,019,408 ("Kourilsky"); Manning et al., "A New Method of In Situ Hybridization," Chromosoma, 53, pp. 107-17 (1975) ("Manning"); Ruth et al., "C-5 Substituted Pyrimidine Nucleosides," J. Org. Chem., 43 (14), pp. 2870-76 (1978) ("Ruth"); Bayer et al., "The Use of The Avidin Biotin Complex As A Tool In Molecular Biology," Methods of Biochemical Analysis, 26, pp. 1-45 (1980) ("Bayer"); and Stryer, Biochemistry (2d Ed.), pp. 348, 512, 589 and 596 (1981) ("Stryer").

("Sodja"), ** pointed to by Examiner Love, refers only to methods of coupling biotin through a cytochrome C bridge to the oxidized 2', 3' terminus of an RNA sugar ring. None of Sodja's compounds suggests the nucleotides or oligo- or polynucleotide sequences of applicants' amended claims 145 and 148-150 because none of Sodja's compounds has a biotin substituent in the base position required in those claims. All of Sodja's compounds have a biotin substituent on the sugar moiety, not on the 5 or 7 position of the base moiety.

For example, applicants' Claim 145 (as amended), and claims dependent thereon, describe nucleotide sequences comprising at least one labelled pyrimidine or 7-deazapurine, wherein a biotin or iminobiotin moiety is attached, either directly or through a linkage group, to the 7-positon of the deazapurine or to the 5-position of the pyrimidine. Applicants' labelled nucleotides are not suggested by Sodja where biotin is attached to the 2', 3' oxidized positions of a sugar ring. Accordingly, amended Claims 145 and 148-150 are patentable over all the documents of record.

Applicants request early allowance of the amended claims.

Respectfully submitted

/s/

James F. Harley, Jr. (Reg. No. 27,794)
Irene J. Frangos (Reg. No. 31,252)
Attorneys for Applicants

** Applicants made this document of record in their Statement Under 37 C.F.R. §§ 1.56 and 1.97, filed June 24, 1985.

c/o FISH & NEAVE
875 Third Avenue, 29th Floor
New York, New York 10022-6250
Tel.: (212) 715-0600

APPENDIX C

OFFICE ACTION OF JULY 2, 1986, U.S. PATENT APPLICATION SERIAL NO. 496,915

EXAMINER'S ACTION

[Seal Omitted]

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
06/496,915	05/23/83	Ward D	18571 A

JAMES F. HALEY, JR.
C/O FISH AND NEAVE
875 THIRD AVENUE 29TH FLOOR
NEW YORK, NY 10022

EXAMINER	
LOVE, E	
ART UNIT	PAPER NUMBER
123	[19]*

DATE MAILED: 07/02/86

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined

☒ Responsive to communication filed on [2/4/86, 3/24/86]

☐ This action is made final.

A shortened statutory period for response to this action is set to expire [3] month(s), _____ [~~days~~] from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

---

* All text in brackets was handwritten in the original.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☐ Notice re Patent Drawing, PTO-948
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims [145, 148-150, 155, 162-164, 166, 171-174, 177, 183, 184, 189-192 and 199] are pending in the application.

   Of the above claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims [145, 148-150, 155, 162-164, 166, 171-174, 177, 183, 184, 189-192 and 199] are rejected.

* * * * *

Serial Number 496,915

Art Unit 123

Claims 145, 148-150, 155, 162-164, 166, 171-174, 177, 183, 184, 189-192 and 199 are in the case.

Claims 145, 148-150, 155, 162-164, 166, 171-174, 177, 183, 184, 189-192 and 199 are again rejected under 35 U.S.C. 112, paragraphs one and two as being too broad with respect to the terminology or recitations "linkage group is characterized by a moiety", "a linkage group not interfering substantially with the characteristic ability of A to form a stable complex with avidin" and "linkage group is characterized by at least one of". [T]he recitations are still indefinite and indeterminable in scope. A markush recitation of linkage groups would be acceptable. See 37 CFR 1.75(d(1).

Claims 145, 148-150, 155, 162-164, 166, 171-174, 177, 183, 184, 189, 192 and 199 are rejected under 35 U.S.C. 102(a) as being anticipated by [and] 35 U.S.C. 103 as being obvious over the Langer et al (II) abstract 1153 and full publication of February 8 to March 20, 1981. The rejection is proper in that the publications are prior to applicants' effective date of April 17, 1981. The references disclose the instant claimed invention or su[b]ject maatter so closely related thereto that the claimed invention would be unpatentable thereover. [illegible handwritten note at the side of this paragraph]

E.G. Loves :dm
(703) 557-3412
June 27, 1986

/s/

Ethel G. Love
Primary Examiner
Art Unit 123

APPENDIX D

AMENDMENT OF DECEMBER 31, 1986, U.S. PATENT APPLICATION SERIAL NO. 496,915

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Ethel G. Love
Group	:	123
Applicants	:	David C. Ward et al.
Serial No.	:	496,915
Filed	:	May 23, 1983
For	:	MODIFIED NUCLEOTIDES AND METHODS OF PREPARING AND USING SAME

New York, New York
December 31, 1986

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

AMENDMENT

Sir:

This is in response to the Office Action dated July 2, 1986 in the above-identified application. Applicants have petitioned concurrently herewith to extend the time for response to that Office Action up to and including January 2, 1987 and have paid the required fee [37 C.F.R. §§ 1.17 and 1.136(a)].

Applicants request amendment of this application as follows:

IN THE CLAIMS

Please amend claims 145, 155, 166, 183 and 199.

* * * * *

Applicants traverse the rejection of Claims 145, 148-50, 155, 162-164, 166, 171-174, 177, 183, 184, 189-192 and 199 under 35 U.S.C. § 112, paragraphs 1 and 2.

The definition of "linkage group" in the amended claims is in no way "indefinite or indeterminable in scope", but rather is finite with a definite boundary. It is fully commensurate with the teachings of this application. It is fully consistent with the use of the term "linking group" in the art. It is also fully supported by numerous actual examples in the application, by examples reported subsequently in the art and by examples actually performed in the laboratories of Enzo Biochem, Inc., the licensee of this application. For all of these reasons, no specific Markush definition of the linkage group is necessary in the amended claims. The amended claims are patentable under 35 U.S.C. § 112.

A compound is defined by its structure and function [In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)]. In the biological sciences, it is well recognized that function is a critical element to describe fully a compound. Accordingly, applicants have provided definitions of both structure and function in their amended claims. The amended claims require a specific structure of a nucleotide, oligonucleotide or polynucleotide and a specific function to define the "linkage group" within the claimed structure. That function is no substantial interference with the characteristic ability of A (biotin or iminobiotin) to form a detectable complex with one of avidin, steptavidin or antibodies to biotin or iminobiotin. Thus, the

claims are fully commensurate with the requirements of the patent laws.

As made plain in this application, the claimed compounds of this invention are characterized by two important biological functions: (1) the oligo- and polynucleotide probes "labelled" with biotin or iminobiotin in accordance with this invention must be able to bind to complementary DNA sequences in an analyte; and (2) after such binding, the biotin or iminobiotin "label" must be detectable by complexing with one of avidin, streptavidin or antibodies to biotin or iminobiotin. The first of these biological functions is accomplished in the claimed invention by applicants' choice of specific labelling positions on a given base for attachment of the biotin or iminobiotin label.

The second of these essential biological functions is a characteristic of applicants' selection of two specific labels – biotin or iminobiotin. These labels have the property of forming detectable complexes with avidin, streptavidin or antibodies to the labels. It is this property that makes applicants' claimed compounds detectable as probes. See, e.g., page 22, line 35 - page 23, line 7:

> "It is clear from the data in these tables that extremely small amounts of biotin can be detected by the method. These results also show that the biotin molecule can be recognized by avidin, streptavidin or specific antibodies while the DNA is still in its native, double-stranded form, a condition that is absolutely essential if the antibody-binding or avidin-affinity approaches are to be useful in probe detection employing hybridization techniques". See also page 9, line 32-page 10, line 2 and page 27, line 26-page 29, line 10.

Thus, the only relevance of the "linkage group" to the claimed compounds and their use as probes is that the "linkage group" not interfere substantially with this property of the biotin and iminobiotin labels. Accordingly, there is no need to limit applicants' claims to one particular Markush group of linkers.

The teaching and disclosure of the application about useful linkers is certainly not limited to a Markush group. Rather, it is fully commensurate with the true scope of applicants' invention -- the biotin or iminobiotin label must be able to form a detectable complex with one of avidin, streptavidin or antibodies. For example, at page 9, line 32- page 10, line 2, the application describes the linker in similar terms to the amended claims:

> "[I]t is preferable that the probe moiety [biotin or iminobiotin] be attached to the purine or pyrimidine [the base] through a chemical linkage or 'linker arm' so that it can readily interact with antibodies, other detector proteins or chemicals reagents."

Apposite also are the many disclosures in the application with respect to the wide range of atoms and functionalities acceptable in a linkage group. E.g.:

> "The linkage group joining moiety A to base B may include any of the well-known bonds including carbon-carbon single bonds, carbon-carbon double bonds, carbon-nitrogen single bonds or carbon-oxygen single bonds" [page 13, lines 10-13].
>
> "[I]t is generally preferred that the chemical linkage include an olefinic bond at the α-position relative to B" [page 13, lines 14-15].
>
> "[Among linkage groups that can be used are] olefin linker arms with other modifiable functionalities

such as thiol, carboxylic acid, and epoxide functionalities" [page 14, lines 2-4].

"It is even more preferred that the chemical linkage group be derived from a primary amine, and have the structure -CH_2-NH-...." [page 13, lines 25-27].

Finally, the examples of specific linkage groups recited in the application confirm that the claimed invention is not limited to particular linkage groups. Those illustrative linkage groups include carbon, hydrogen, nitrogen and oxygen atoms. They also include carbon-carbon single and double bonds, carbon-nitrogen single bonds, carbon-hydrogen single bonds and carbon-oxygen single bonds. E.g., -CH=CH-CH_2-NH- and

$$CH=CH\text{-}CH_2\text{-}O\text{-}CH_2\text{-}\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}CH_2\text{-}NH\text{-}$$

(page 18, line 31).

Thus, the application itself never suggests that the described invention is limited to a specific Markush group of linkers. There is, therefore, no reason for the claims to be narrower than that invention.

In addition to being completely supported by this application, the definition of "linkage group" in the amended claims is also fully consistent with a wide variety of illustrative linkage groups actually demonstrated or reported to be useful in preparing compounds within applicants' claims.

As suggested by Examiner Love during the July 30, 1986 interview, applicants now make of record eight of these linkage groups by listing them in Exhibit A to the Declaration Of Dean L. Engelhardt Under 37 C.F.R. § 1.132, filed concurrently herewith ("Engelhardt Declaration"). These linkage groups conform structurally and

functionally to the description in the specification and the definition of the amended claims. They contain carbon, nitrogen, hydrogen, oxygen and sulfur atoms. They contain carbon-carbon single and double bonds, carbon-nitrogen single bonds, carbon-oxygen single and double bonds, carbon-hydrogen single bonds, carbon-sulfur single bonds and sulfur-sulfur single bonds. They also contain heterocylic and aromatic rings. And, they include straight chains of from 4 to 16 atoms in length. Yet, none of these diverse linkers functionally interfere with the ability of biotin in an olgio- or polynucleotide probe of this invention to form a detectable complex with one of avidin, streptavidin or antibodies to biotin. The demonstrated consistent utility of this wide structural variety of linkage groups in the compounds of this invention supports a single conclusion -- there is no reason to limit the "linkage group" of applicants' claimed compounds to a single Markush group.

* * * * *

APPENDIX E

OFFICE ACTION OF APRIL 16, 1987, U.S. PATENT APPLICATION SERIAL NO. 496,915

EXAMINER'S ACTION

[Seal Omitted]

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
06/496,915	05/23/83	Ward D	18571-A

JAMES F. HALEY, JR.
C/O FISH AND NEAVE
875 THIRD AVENUE 29TH FLOOR
NEW YORK, NY 10022

EXAMINER	
CHAN, N	
ART UNIT	PAPER NUMBER
123	[24]*

DATE MAILED: 04/16/87

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined

☒ Responsive to communication filed on [1/5/87]

☒ This action is made final.

A shortened statutory period for response to this action is set to expire [3] month(s), _____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

---

* All text in brackets was handwritten in the original.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☐ Notice re Patent Drawing, PTO-948
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims [145, 148-150, 155, 162-164, 166, 171-174, 177, 179-181, 183-184, 189-192, and 199] are pending in the application.

   Of the above claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims [145, 148-150, 155, 162-164, 166, 171-174, 177, 179-181, 183-184, 189-192 and 199] are rejected.

* * * * *

Serial Number 496915

Art Unit 123

Claims 145, 148-150, 155 162-164, 166, 171-174, 177, 179-181, 183, 184, 189-192 and 199 are in the case.

Applicant's arguments filed January 5. 1987 have been fully considered but they are not deemed to be persuasive.

Claims 145, 148-150, 155, 162-164, 166, 171-174, 177, 179-181, 183-184, 189-192 and 199, all of the claims in case, are rejected under 35 U.S.C. 102 (a) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over [La]nger et al abstract 1153.

This symposium abstract evidences that the claimed invention [was] known by other in this country before the invention thereof by the applicant.

A declaration under 37 CFR 1.131 as offered by applicant will obviate this rejection.

Claims 177, 179-180 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 177, the word "deazaadenine" is misspelled. [not in cl 17. Told Oster to forget it. 6/1/87]

In claim 179, the recitation of A as "as second moiety" is confusing because A is included in the "first moiety". The word "second" shoudl be deleted.

A bond connecting the OH group is missing.

The specification should be amended to reflect the status of the parent application and should be reviewed for any minor errors.

Serial Number 496915

Art Unit 123

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Nicky Chan whose telephone number is (703) 557-0367.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 557-3920.

NChan:cc
4-14-87

/s/
Nicky Chan
Primary Examiner
Art Unit 123

APPENDIX F

LETTER OF MARCH 7, 1995 FROM DR. STEPHEN MACEVICZ TO HON. LAWRENCE J. GOFFNEY, ASSISTANT COMMISSIONER OF PATENTS

PERKIN ELMER

Applied Biosystems Division
850 Lincoln Centre Drive
Foster City, CA 94404

7 March 1995

VIA FACSIMILE **7 PAGES IN TRANSMISSION**

Hon. Lawrence J. Goffney, Jr.
Assistant Commissioner of Patents
U.S. Department of Commerce
Washington, D.C. 20231

Subject: **SUBMARINE PATENT APPLICATION, a continuation of Ward et al, USSN 06/496,915 filed 23 May 1983 (Ward I) and/or Ward et al, USSN 07/130,070 filed 8 December 1987 (Ward II) (Cover sheets attached)**

Dear Sir:

It was a pleasure meeting with you and several of my colleagues from Silicon Valley last Friday, March 3. We were very encouraged by your remarks and your commitment to improving Patent Office performance. I personally very much appreciated the opportunity to tell you

about the particular difficulty that my company is facing because of a Patent Office "quality control" issue.

In this communication, I want to re-iterate my concern and again ask if something could be done to address this concern *inside the Patent Office* prior to the issuance of a third Ward patent. I greatly fear that a mis-application of patentability standards is leading my company into a grossly unfair multi-million dollar patent infringement suit. My concern about the Ward application is summarized below:

SOURCE OF CONCERN:

Letter from Enzo Biochem stating that the U.S. Patent Office issued a Notice of Allowance for Claim 195 attached as Exhibit A.

This claim covers fluorescently labeled DNA sequencing fragments (formula in terms of Claim 195 shown on Exhibit B), a key component in all presently and foreseeably available automated DNA sequencing procedures and instruments--that is, a fundamental technology upon which all genome sequencing projects rely.

This is a $200M+ per year business, largely built by Applied Biosystems. Many small-to-medium-sized biotech instrumentation companies, besides Applied Biosystems, would be severely damaged by the issuance of Claim 195, or like claims.

WHAT IS THE PATENTABILITY ISSUE:

Claim 195 combines disparate elements of the original disclosure (and invention) to create a new compound not described in the specification as required under 35 U.S.C. 112 first paragraph. **This newly described compound inappropriately covers DNA sequencing fragments.** No prior claim of the application or passage in the

specification describes compounds that cover DNA sequencing fragments.

The most compelling facts of this situation are illustrated by the time line of Exhibit C: The original Ward application was filed nearly four years prior to the invention of fluorescent DNA sequencing. Nothing in any of the Ward specifications, the prosecution up to 1994, or pending claims up to 1994 give any indication that the invention includes compounds covering DNA sequencing fragments. It is only after the industry grew from $0 in sales to over $200 million in sales between 1986 and 1995 that a claim appeared in a recent continuation application that sought to cover DNA sequencing fragments! These facts are characteristic of the so-called SUBMARINE PATENT phenomena.

* * * * *

I hope you find the above information and explanations helpful. Our industry would greatly appreciate any help you could provide in rectifying this unfortunate situation.

With best regards,

/s/

Stephen C. Macevicz
Senior Patent Attorney

Attachments
cc: Dr. Michael Hunkapiller
Vice President

(7)

No. 10-426

Supreme Court, U.S.
FILED
MAY 31 2011
OFFICE OF THE CLERK

IN THE
Supreme Court of the United States

APPLERA CORP. AND TROPIX, INC.,
Petitioners,

v.

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., AND YALE UNIVERSITY,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

SUPPLEMENTAL BRIEF

NICHOLAS GROOMBRIDGE
JENNIFER H. WU
WEIL, GOTSHAL & MANGES LLP
767 Fifth Avenue
New York, NY 10153
(212) 310-8000

ANTON J. BOKAL
ALAN W. HAMMOND
KURTIS D. MACFERRIN
LIFE TECHNOLOGIES CORP.
850 Lincoln Centre Drive
Foster City, CA 94404
(650) 554-3410

CARTER G. PHILLIPS*
ERIC A. SHUMSKY
RACHEL TOWNSEND
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, DC 20005
(202) 736-8000
cphillips@sidley.com

TACY F. FLINT
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, IL 60603
(312) 853-7000

JOHN M. WHEALAN
4613 Merivale Road
Chevy Chase, MD 20815
(202) 994-2195

Counsel for Petitioners

May 31, 2011 *Counsel of Record

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20002

TABLE OF CONTENTS

	Page
TABLE OF AUTHORITIES	ii
SUPPLEMENTAL BRIEF	1
I. THE FEDERAL CIRCUIT HAS DEPARTED FROM THE TEXT OF § 112 AND THIS COURT'S PRECEDENTS CONSTRUING IT	2
II. THE FEDERAL CIRCUIT'S INTERPRETATION OF § 112 CONFLICTS WITH THE PTO'S	7
III. THE DECISION BELOW IS A GOOD VEHICLE FOR RESOLVING THESE ISSUES	8
CONCLUSION	12

TABLE OF AUTHORITIES

CASES Page

Bancorp Servs. v. *Hartford Life Ins.*, 359 F.3d 1367 (Fed. Cir. 2004) 5
Bd. of Regents v. *BENQ Am. Corp.*, 533 F.3d 1362 (Fed. Cir. 2008) 5
In re Corkill, 771 F.2d 1496 (Fed. Cir. 1985) 6
Datamize v. *Plumtree Software*, 417 F.3d 1342 (Fed. Cir. 2005) 2, 7
eBay v. *MercExchange*, 547 U.S. 388 (2006) 10
Energizer Holdings v. *ITC*, 435 F.3d 1366 (Fed. Cir. 2006) 5
Exxon Research & Eng'g v. *United States*, 265 F.3d 1371 (Fed. Cir. 2001) 2, 3, 4
The Incandescent Lamp Patent, 159 U.S. 465 (1895) 2
KSR Int'l v. *Teleflex*, 550 U.S. 398 (2007) 7, 10
Markman v. *Westview Instrs.*, 517 U.S. 370 (1996) 2
Phillips v. *AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) 5
Power-One v. *Artesyn Techs.*, 599 F.3d 1343 (Fed. Cir. 2010) 4
United Carbon v. *Binney & Smith*, 317 U.S. 228 (1942) 1
Young v. *Lumenis*, 492 F.3d 1336 (Fed. Cir. 2007) 5

STATUTE AND REGULATION

35 U.S.C. § 112 ¶ 2 2

TABLE OF AUTHORITIES—continued

Page

Supplementary Examination Guidelines for Determining Compliance With 35 U.S.C. 112 and for Treatment of Related Issues in Patent Applications, 76 Fed. Reg. 7162 (Feb. 9, 2011) 4, 7, 8, 9

OTHER AUTHORITIES

Fed. Trade Comm'n, *The Evolving IP Marketplace* (Mar. 2011), *available at* http://www.ftc.gov/os/2011/03/110307patentreport.pdf 3, 4, 7

PatStats.org, *U.S. Patent Litigation Statistics*, http://www.patstats.org/Patstats2.html (last viewed May 25, 2011) 6

SUPPLEMENTAL BRIEF

If the Federal Circuit actually used the indefiniteness standard that the United States articulates, we would not be here today. The government recognizes that the Patent Act "requir[es] that patent claims provide clear notice of the metes and bounds of the patented invention." U.S. Br. 8. Strikingly, this is the same legal standard articulated by Applera, and it is grounded in this Court's precedents holding that the inventor must specify the invention's boundaries so that the public can understand precisely what is reserved to the patentee, Pet. 16-18. The government, however, misapprehends the Federal Circuit's actual practice. The problem is not "phrases" that are troubling "in isolation," U.S. Br. 13, nor the occasional "misapplication" of a correct legal standard, *id.* at 15. What is required is a course correction: The Federal Circuit does not remotely require the "clarity," "precision" and "particular[ity]" that this Court has recognized the Patent Act demands. This error has given rise to a fundamental imbalance in the patent system. Because the Federal Circuit almost always finds patent claims definite under its toothless standard, there exists a substantial incentive for patentees to draft their claims broadly and vaguely. The result—as Judge Plager explains, and Professor Lemley confirms on behalf of leading innovators—is that competition is stifled. Pet. App. 76a n.2; Altera Br. 11 & n.3, 13, 15-17. This is the very "zone of uncertainty" that the Court has warned of. *United Carbon* v. *Binney & Smith*, 317 U.S. 228, 236 (1942). It is this essential malfunction—and not some quibble about terminology—that cries out for correction.

I. THE FEDERAL CIRCUIT HAS DEPARTED FROM THE TEXT OF § 112 AND THIS COURT'S PRECEDENTS CONSTRUING IT.

For more than a century, the Court has recognized that the Patent Act demands "clarity," "precision" and "particular[ity]" in patent claims. 35 U.S.C. § 112 ¶ 2 ("particularly pointing out and distinctly claiming"); *Markman* v. *Westview Instrs.*, 517 U.S. 370, 390 (1996) (public must be "'clearly told what ... limits [its] rights'"); *The Incandescent Lamp Patent*, 159 U.S. 465, 475 (1895) ("'clearness and precision'"); see Pet. 16-18 (citing cases). Far from disputing these standards, the United States reiterates them. U.S. Br. 8.

The Federal Circuit's test resides at the other end of the claiming spectrum. See Pet. 18-21. Rather than requiring "clarity" and "precision," the Federal Circuit says that a claim is indefinite "only if reasonable efforts at claim construction *prove futile*." *Exxon Research & Eng'g* v. *United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001) (emphasis added). Alternatively: "Only claims 'not amenable to construction' or 'insolubly ambiguous'"—that is, whose terms "*can[not] be given any reasonable meaning*"—"are indefinite." *Datamize* v. *Plumtree Software*, 417 F.3d 1342, 1347 (Fed. Cir. 2005) (emphasis added). The government sheepishly acknowledges the error in the Federal Circuit's jurisprudence:

> Read in isolation, those phrases ["capable of construction" and not "insolubly ambiguous"] might suggest an insufficiently demanding definiteness standard to a district court looking for guidance. At least in the main run of its decisions, however, the Federal Circuit has used those phrases to express principles that are well grounded in this Court's Section 112 jurisprudence.

U.S. Br. 13; *accord id.* at 15. Not only "might" the Federal Circuit's cases "suggest" an erroneous standard—the United States previously has recognized that they do just that. It has compared the Federal Circuit's leading indefiniteness case unfavorably with this Court's cases,[1] and the Federal Trade Commission criticized "the 'insolubly ambiguous' standard" for "accept[ing] substantial ambiguity."[2] The government's recognition that the court of appeals with exclusive jurisdiction over patent cases employs a test that may mislead district courts is proof positive that this Court should grant review.

The government nonetheless says that certiorari should be denied because the Federal Circuit is using this "imprecise language" as a stand-in for correct "principles"—not always, but "in the main run of its decisions." U.S. Br. 12-13. In fact, the Federal Circuit's rule conflicts directly with "this Court's Section 112 jurisprudence." The United States devotes multiple pages to showing that the Federal Circuit correctly articulates certain claim-construction principles, both in general, *id.* at 8-9, and in this case, *id.* at 11, 15 (quoting Pet. App. 11a). But rules of claim construction are not at issue here; this petition asks the Court to review the Federal Circuit's erroneous understanding of indefiniteness. And, at least since the Federal Circuit announced its "insolubly ambiguous" test in 2001, see *Exxon Research*, 265 F.3d at 1375,[3] that court has required minimal determinacy

---

[1] *See* Pet. 25 (quoting U.S. amicus brief in *Ariad Pharm.* v. *Eli Lilly*).

[2] *The Evolving IP Marketplace* 11 (Mar. 2011), *available at* http://www.ftc.gov/os/2011/03/ 110307patentreport.pdf.

[3] The government's reliance on earlier Federal Circuit cases, Br. 12-13, therefore is beside the point.

in patent claims. Its test cannot be dismissed as "imprecise language," U.S. Br. 12—the Federal Circuit has employed it some 30 times since 2001.[4] The FTC correctly recognizes that "[t]he Federal Circuit requires that claims be 'insolubly ambiguous' to be invalid as indefinite." *The Evolving IP Marketplace*, *supra*, at 11. And, contrary to what it says here, the PTO recognizes elsewhere that *Exxon* imposes a low threshold: "[T]he validity of a claim will be preserved if *some meaning* can be gleaned from the language."[5]

Exxon, the substance of which the government does not address, confirms that the Federal Circuit meant what it said. There, the court held that the term "for a period sufficient" was definite—even though the patent did not "quantify the 'period sufficient' limitation by reference to any specific period or range of periods," 265 F.3d at 1378—because the patent provided one example that satisfied this broad language, *id.* at 1378-79. The claims in *Exxon* did not establish "metes and bounds," much less by "clear notice." The government therefore is wrong that "[t]he Federal Circuit has most frequently used the relevant phrases"—i.e., "capable of construction" and "insolubly ambiguous"—"to express the insight that a patent claim may be sufficiently definite ... even though considerable study and analysis are required to discern its meaning." U.S. Br. 13. Rather, the Federal Circuit means by these "phrases" that claims are only indefinite in the extreme case when they provide "no guidance," *Power-One* v. *Artesyn Techs.*, 599 F.3d 1343,

---

[4] Search of Westlaw's Federal Circuit database (CTAF) for all cases with "insolub!" and "ambig!" in the same sentence.

[5] Supplementary Examination Guidelines for Determining Compliance With 35 U.S.C. 112 and for Treatment of Related Issues in Patent Applications, 76 Fed. Reg. 7162, 7164 (Feb. 9, 2011) ("*PTO Guidelines*") (emphasis added).

1348 (Fed. Cir. 2010), and cannot "'be given any reasonable meaning,'" *Young* v. *Lumenis*, 492 F.3d 1336, 1346 (Fed. Cir. 2007).

This test is so firmly entrenched that the Federal Circuit has developed corollary doctrines based on it. Thus, the decision below holds that "a claim cannot be both indefinite and anticipated" because "[i]f a claim is indefinite, the claim, by definition, cannot be construed" and "[w]ithout a discernable claim construction, an anticipation analysis cannot be performed." Pet. App. 10a. By its terms, this analysis ties indefiniteness to whether claim language is capable of construction. The problem with doing so—as the Petition explains and the government does not address—is that claim construction does not necessarily identify the invention's "metes and bounds." Pet. 18-19. Claim construction commonly focuses on individual claim terms, not the claim as a whole. Sometimes the most a court can do is to define a claim term with a synonym, which is what happened here. See *id.* at 19; Pet. App. 52a; CAFC JA 44. Claim construction incorporates no requirement of definiteness—it simply asks the court to determine how a person of ordinary skill in the art understands disputed claim terms. *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). The fact that a claim term has been construed therefore does not mean the claim is definite, contrary to the Federal Circuit's erroneous understanding.[6]

---

[6] *E.g.*, *Bd. of Regents* v. *BENQ Am. Corp.*, 533 F.3d 1362, 1368 n.4 (Fed. Cir. 2008) (no indefiniteness where "we have been able to discern a construction"); *Energizer Holdings* v. *ITC*, 435 F.3d 1366, 1370-71 (Fed. Cir. 2006) ("A claim that is amenable to construction is not ... indefinite[]."); *Bancorp Servs.* v. *Hartford Life Ins.*, 359 F.3d 1367, 1372 (Fed. Cir. 2004) (same).

Ultimately, the proof is in the cases, and a survey shows that the Federal Circuit almost never finds indefiniteness. Of 48 indefiniteness decisions since *Exxon*, that court found indefiniteness only five times.[7] There is no reported case in the past 10 years in which the Federal Circuit affirmed a PTO determination that a patent claim is indefinite, and only one since the formation of the Federal Circuit in 1982.[8] In stark contrast, since 2000 the Federal Circuit has ruled for litigants asserting invalidity under 35 U.S.C. § 102(b), § 103, and § 112 doctrines other than indefiniteness between 41% and 54% of the time.[9] The amici supporting Applera's petition confirm that indefiniteness is a dead letter, as does a recent review of district court decisions. Altera Br. 11 & n.3 (discussing study by Laser). It is no wonder that Enzo could not identify a single meaningful application of definiteness by the Federal Circuit. BIO 27; see Reply Br. 7.

In short, the government has matters backwards. This is not a situation in which the Federal Circuit occasionally uses "imprecise" language while generally interpreting and applying the law properly. On the contrary, the Federal Circuit occasionally states the law correctly, see U.S. Br. 14-15, but most of the time it does not, and in application it almost never finds a claim indefinite. Following a pattern seen in other

---

[7] Search of CTAF database for all cases with "claim!" and "indefinite!" in the same sentence; we excluded cases involving a technical indefiniteness defect such as failure to comply with 35 U.S.C. § 112 ¶ 6.

[8] *In re Corkill*, 771 F.2d 1496, 1500-01 (Fed. Cir. 1985). Search of CTAF for all appeals from the PTO since 2001 that include the term "indef!"

[9] Statistics compiled from the University of Houston's patent statistics database, http://www.patstats.org/Patstats2.html.

cases, the Federal Circuit took an accurate statement of law—that insolubly ambiguous claims are indefinite—and rewrote it into an exclusive test that is erroneous: "*Only* claims 'not amenable to construction' or 'insolubly ambiguous' are indefinite." *Datamize*, 417 F.3d at 1347 (emphasis added). The Court has corrected such errors before, and should do so here. *KSR Int'l* v. *Teleflex*, 550 U.S. 398, 415, 418-19 (2007) ("We begin by rejecting the rigid approach of the Court of Appeals."; "Helpful insights ... need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents."). It is broadly understood among patent lawyers that indefiniteness has drifted into desuetude, an intolerable state of affairs that incentivizes broad and imprecise claim drafting to the detriment of the public. Review is appropriate now and in this case: "If this Court does not act, there will be little or no incentive for future litigants to raise the issue in the lower courts." Altera Br. 18-19.

II. THE FEDERAL CIRCUIT'S INTERPRETATION OF § 112 CONFLICTS WITH THE PTO'S.

The petition demonstrates that the PTO and the Federal Circuit employ different tests for indefiniteness. Pet. 23-26; Reply 8-9. The government responds that "the PTO's recently published guidelines for examiners ... make clear [that] the agency conducts essentially the same definiteness inquiry that courts apply." U.S. Br. 16. But the PTO Guidelines actually say something quite different: "Claims under examination are evaluated with a different standard than patented claims to determine whether the language is definite." 76 Fed. Reg. at 7164 (capitalization and emphasis omitted). The FTC agrees. See *The Evolving IP Marketplace*, *supra*, at 11 ("[t]he

PTO ... has adopted a lower threshold of ambiguity"). This is why the government must admit that "[t]he PTO does instruct agency examiners to employ 'a lower threshold of ambiguity when reviewing a pending claim for indefiniteness' than that used by the Federal Circuit." U.S. Br. 17.

Moreover, the PTO recognizes elsewhere that the Federal Circuit is not using the standard that the government advocates here. The *PTO Guidelines* say that a claim should be rejected during examination "if the metes and bounds of the claimed invention are not clear." 76 Fed. Reg. at 7164. That is the standard that the government says should govern in the Federal Circuit, see U.S. Br. 8, yet the PTO says in its *Guidelines* that the Federal Circuit is employing a less demanding standard. 76 Fed. Reg. at 7164. Paradoxically, the government also seeks to justify the use of disparate standards, U.S. Br. 17—an assertion at odds with its claim that the PTO and the Federal Circuit are using the same standard, *id.*—but the PTO and the Federal Circuit are applying the same statutory language, and in no other domain does the PTO assert that its legal test can diverge from the Federal Circuit's. See Pet. 24 & n.10; Reply 8-9. Plainly, the language of the statute does not have a different meaning depending whether it is to be applied in the PTO or the courts. This stark inconsistency confirms that clarity from this Court is sorely needed.

III. THE DECISION BELOW IS A GOOD VEHICLE FOR RESOLVING THESE ISSUES.

As the petition explains, this case presents a striking application of the Federal Circuit's standard. Pet. 26-29. The patents employ broad functional language and terms of degree—techniques this Court and the PTO warn are particularly susceptible to indefinite-

ness—at the very point of alleged novelty. *Id.* at 27 & n.12; *PTO Guidelines*, 76 Fed. Reg. at 7164-65. Rather than providing "clear notice" of "metes and bounds," these patents give mere examples. Pet. 11-12, 21-22, 26-27. This, presumably, is why Enzo felt compelled to argue that definiteness does not require clear notice of boundaries. BIO 15 (claims need not "fix the 'metes and bounds' of the invention"); *accord id.* at 3, 12, 16. Instead, Enzo advances the novel argument that patent claims merely distinguish an invention from the prior art. *Id.* at 2-3. Tellingly, the government does not defend Enzo's unprecedented rule, and the formulation embraced by the government—"clear notice of the [invention's] metes and bounds," U.S. Br. 8—is flatly at odds with Enzo's.

Instead, the government responds that this case is an unsuitable vehicle because "the court of appeals did not use either the phrase 'insolubly ambiguous' or the phrase 'capable of construction.'" U.S. Br. 15. This argument is curious, given the government's insistence that the focus should be on underlying "principles" rather than "those phrases." *Id.* at 13. In any event, the court indeed embraced these concepts: It held that "[i]f a claim is indefinite, the claim, by definition, cannot be construed," and on that basis developed a false syllogism that anticipation is impossible where there is indefiniteness. Pet. App. 10a. Moreover, the court relied on established Federal Circuit authorities which hold that claims are indefinite only when they are "not amenable to construction or are insolubly ambiguous." Reply Br. 6 (quotation marks omitted). More egregious still, the court was satisfied because the claims "provide at least some guidance," Pet. App. 14a—a far cry from "particularly pointing out and distinctly claiming."

The government further cautions the Court to avoid the "highly technical" facts of this case, U.S. Br. 15, vouching that one of ordinary skill in the art would understand the claims, *id.* at 18-22. This is wrong for the reasons we have explained, see Pet. 26-29, and it is beside the point. The issue here is the erroneous legal standard that controls in the Federal Circuit, and it is that fundamental legal error that warrants this Court's time and attention. Just as it did in *eBay* and *KSR*,[10] the Court should grant certiorari to correct the Federal Circuit's erroneous test for a key patent law doctrine and—as it did in *eBay* and has done in numerous cases in other contexts—the Court may remand for the lower courts to apply that standard in this case.

In any event, this case is particularly suitable for review because it is the unusual instance in which a district court did hold claims indefinite. The court reviewed Enzo's own expert testimony explaining that "'[i]t's probably in the hands of the experimenter'" to determine the bounds of substantiality, a boundary that "'may mean different things to different people.'" Pet. App. 57a; *id.* at 60a. The court understandably found it "instructive" that two scientists, both Enzo executives, could not "conjecture a means of determining substantiality of interference." *Id.* at 56a, 58a. Most telling, Enzo employed different experts for infringement and validity, who took conflicting views on the reach of the claim term—one interpreting it broadly to capture infringement, the other narrowly to avoid invalidity, *id.* at 64a—which is a tactic that has become common because of the Federal Circuit's indefiniteness doctrine, see Yahoo

---

[10] *See KSR*, 550 U.S. 398; *eBay* v. *MercExchange*, 547 U.S. 388 (2006).

Br. 14-16. The court construed the claim terms, while correctly recognizing them to be an "illusory yardstick." Pet. App. 60a. Enzo dared the court to find the terms indefinite—"[T]he Court should faithfully interpret 'substantially interfering' and if it's indefinite, then we'll have to live with that," CAFC JA 1644-47—and the district court was the rare one to do so.

"For a decade," Enzo acknowledges, "the Federal Circuit has employed its current standards without meaningful dispute or dissent." BIO 25. And this Court has not directly considered definiteness since World War II. The patent community is watching this case to see whether the last nail is in the coffin. Patent practitioners, litigants, the public and innovation all will suffer if it is no longer possible to tell with meaningful clarity what a patent claim covers.

CONCLUSION

For the foregoing reasons, and those set forth in the petition and reply brief, the petition for a writ of certiorari should be granted.

Respectfully submitted,

NICHOLAS GROOMBRIDGE
JENNIFER H. WU
WEIL, GOTSHAL & MANGES LLP
767 Fifth Avenue
New York, NY 10153
(212) 310-8000

ANTON J. BOKAL
ALAN W. HAMMOND
KURTIS D. MACFERRIN
LIFE TECHNOLOGIES CORP.
850 Lincoln Centre Drive
Foster City, CA 94404
(650) 554-3410

CARTER G. PHILLIPS*
ERIC A. SHUMSKY
RACHEL TOWNSEND
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, DC 20005
(202) 736-8000
cphillips@sidley.com

TACY F. FLINT
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, IL 60603
(312) 853-7000

JOHN M. WHEALAN
4613 Merivale Road
Chevy Chase, MD 20815
(202) 994-2195

Counsel for Petitioner

*Counsel of Record

May 31, 2011

175 (4)
No. 10-426
FILED
NOV 22 2010
OFFICE OF THE CLERK

IN THE
Supreme Court of the United States

APPLERA CORP. AND TROPIX, INC.,
Petitioners,

v.

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., AND YALE UNIVERSITY,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

REPLY BRIEF

NICHOLAS GROOMBRIDGE
JENNIFER H. WU
WEIL, GOTSHAL & MANGES LLP
767 Fifth Avenue
New York, NY 10153
(212) 310-8000

ANTON J. BOKAL
ALAN W. HAMMOND
KURTIS D. MACFERRIN
LIFE TECHNOLOGIES CORP.
850 Lincoln Centre Dr.
Foster City, CA 94404
(650) 554-3410

CARTER G. PHILLIPS*
ERIC A. SHUMSKY
RACHEL TOWNSEND
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, DC 20005
(202) 736-8000
cphillips@sidley.com

TACY F. FLINT
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, IL 60603
(312) 853-7000

JOHN M. WHEALAN
12 Sunnyside Road
Silver Spring, MD 20910
(202) 994-2195

Counsel for Petitioners

November 22, 2010 *Counsel of Record

WILSON-EPES PRINTING CO., INC – (202) 789-0096 – WASHINGTON, D C 20002

TABLE OF CONTENTS

	Page
TABLE OF AUTHORITIES	ii
REPLY BRIEF	1
ARGUMENT	2
I. THE FEDERAL CIRCUIT HAS DEPARTED FROM THE TEXT OF § 112 AND THIS COURT'S PRECEDENTS CONSTRUING IT	2
II. THE FEDERAL CIRCUIT'S INTERPRETATION OF § 112 CONFLICTS WITH THE PTO'S	8
III. THE DECISION BELOW IS AN EXCELLENT VEHICLE FOR RESOLVING THESE ISSUES	9
CONCLUSION	12

TABLE OF AUTHORITIES

CASES Page

Acacia Media Techs. Corp. v. *New Destiny Internet Grp.*, No. 05—CV-114. MDL Case No. 05-1665 (N.D. Cal. Oct. 23, 2009), *aff'd*, No. 2010-1081 (Fed. Cir. Oct. 7, 2010) 7
Datamize, LLC v. *Plumtree Software*, 417 F.3d 1342 (Fed. Cir. 2005) 6
Eibel Process v. *Minn. & Ont. Paper*, 261 U.S. 45 (1923) 4, 5
Festo Corp. v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002) 3, 5
Gen. Elec. v. *Wabash Appliance Corp.*, 304 U.S. 364 (1938) 3
Keystone Bridge v. *Phoenix Iron*, 95 U.S. 274 (1877) 9
KSR Int'l v. *Teleflex*, 550 U.S. 398 (2007) 7, 11
Markman v. *Westview Instr.*, 517 U.S. 370 (1996) 3
McClain v. *Ortmayer*, 141 U.S. 419 (1891) 4
Merrill v. *Yeomans*, 94 U.S. 568 (1876) 9
Ex parte Miyazaki, No. 2007-3300, 2008 WL 5105055 (B.P.A.I. Nov. 19, 2008) 9
Permutit v. *Graver Corp.*, 284 U.S. 52 (1931) 3
Phillips v. AWH Corp. 415 F.3d 1303 (Fed. Cir. 2005) 4
Quantum Corp. v. *Rodime*, 65 F.3d 1577 (Fed. Cir. 1995) 7
United Carbon v. *Binney & Smith Co.*, 317 U.S. 228 (1942) 3, 5
Warner-Jenkinson v. *Hilton Davis Chem.*, 520 U.S. 17 (1997) 5

TABLE OF AUTHORITIES—continued

Page

White v. *Dunbar*, 119 U.S. 47 (1886) 3

Young v. *Lumenis*, 492 F.3d 1336 (Fed. Cir. 2007) 6

STATUTES

35 U.S.C. § 112 1

§ 251 9

SCHOLARLY AUTHORITIES

Eugene Gressman et al., *Supreme Court Practice* (9th ed. 2007) 11

S. Jay Plager, *The Federal Circuit As An Institution: Of Uncertainty and Policy Levers*, 43 Loyola L.A. L. Rev. 749 (2010) 8

OTHER AUTHORITY

FTC, *To Promote Innovation: The Proper Balance Of Competition and Patent Law and Policy* (2003), *available at* http://www.ftc.gov/os/2003/10/innovationrpt.pdf 8

REPLY BRIEF

Applera's petition demonstrates that the Federal Circuit's standard for indefiniteness—under which a patent's claims need merely be "capable of construction" and therefore not "insolubly ambiguous," Pet. 18-22—is fundamentally inconsistent with 35 U.S.C. § 112, which requires that claims be "particular[ ]" and "distinct[ ]." Whereas this Court requires "precision" and clarity, Pet. 16-18, here, the Federal Circuit was satisfied with merely "some guidance," Pet. App. 14a. Enzo says little about the question actually presented by the petition. It does not deny that the "capable of construction" test governs in the Federal Circuit. It does not even deny that that test is inconsistent with this Court's precedents.

Instead, Enzo answers a different question entirely—whether § 112 "precludes the use of relative terms." BIO i. This argument is the heart of Enzo's case against certiorari, see *infra* at 5, but that question is not remotely presented. The petition nowhere suggests that words of degree are indefinite per se—and of course not; Applera's own patents use such terms, BIO 25-26—which is why Enzo never once provides a page citation to the petition in attacking this straw man. Its other principal argument is that patent claims do not define an invention. See *infra* at 2-5. Over a century of this Court's cases hold otherwise. That the Federal Circuit's jurisprudence has reached the point where a litigant could make this argument with a straight face is the best evidence of the need for this Court's review.

The real question presented is whether the Federal Circuit's approach to a critical patent doctrine has departed, again, from the words of the statute. It has, and review is sorely needed. This question is vi-

tally important, as the amici supporting Applera have explained, and it is recurring—it governs every patent's validity and construction. The Federal Circuit's standard is at odds with the statute's text and purposes, and this Court's precedents interpreting it, and has been rejected by the PTO and called into question by the Department of Justice. The petition should be granted.

ARGUMENT

I. THE FEDERAL CIRCUIT HAS DEPARTED FROM THE TEXT OF § 112 AND THIS COURT'S PRECEDENTS CONSTRUING IT.

Enzo does not attempt to reconcile the Federal Circuit's indefiniteness standard with the statutory text. It does not defend the "capable of construction" test, nor the "insolubly ambiguous" iteration of it. Instead, it offers a vision of patent claiming so radical that it confirms the case for certiorari, and addresses questions that are not presented.

1. Enzo turns to the "origins" of the claiming requirement to argue that the inventor need not inform the public of an invention's boundaries, but must only distinguish the claimed invention from the prior art. BIO 2-3, 12, 17-20. Even if this argument were correct, and it is not, Enzo never explains how it would support the Federal Circuit's "capable of construction" test. It therefore is no argument against certiorari.

On its merits, this argument is contrary to the most basic requirements of the Patent Act. Never has this Court held that a patent's only purpose is to distinguish the claimed invention from the prior art. Rather, the claims serve a fundamental notice function: "The inventor must 'inform the public during the life of the patent of *the limits of the monopoly as-*

serted....'" *Gen. Elec.* v. *Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938).[1] This is so everyone will know "which features may be safely used or manufactured without a license and which may not." *Permutit* v. *Graver Corp.*, 284 U.S. 52, 60 (1931).

Accordingly, the claims must *both* distinguish the invention from the prior art and demarcate the invention's boundaries: "The statutory requirement of particularity and distinctness in claims is met only when they clearly distinguish what is claimed from what went before in the art *and* clearly circumscribe what is foreclosed from future enterprise." *United Carbon* v. *Binney & Smith*, 317 U.S. 228, 236 (1942). Enzo does not explain what purpose would be served by a patent that does not tell the public what the invention is, a notion counter to both common sense and this Court's decisions. *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002) ("A patent holder should know what he owns, and the public should know what he does not."); *GE*, 304 U.S. at 369 (the "limits of a patent must be known").

The extreme nature of Enzo's argument is laid bare by its attack on the claiming requirement. It derides as "court-made" the requirement "that the claims 'define' the invention." BIO 20. That is not this Court's view, which explained 125 years ago that "[t]he claim is a statutory requirement, prescribed for the very purpose of making the patentee define precisely what his invention is." *White* v. *Dunbar*, 119 U.S. 47, 52 (1886); see *Markman* v. *Westview Instr.*, 517 U.S. 370,

---

[1] Emphases added throughout unless otherwise noted.

373 (1996) ("[t]he claim 'define[s] the scope of a patent grant'").[2]

Cases like *Permutit* and *GE* demonstrate the error in Enzo's argument that patent claims need not provide "a blueprint for circumvention." BIO 1, 17, 19. The claims indeed are meant to give the public clear notice of "which features may be safely used or manufactured without a license and which may not." *Permutit*, 284 U.S. at 60. While Enzo denigrates this as a "blueprint for circumvention," its own principal authority explains that "[i]ndefiniteness is objectionable because the patent does not disclose to the public how the discovery ... can be made useful *and how its infringement may be avoided*." *Eibel Process* v. *Minn. & Ont. Paper*, 261 U.S. 45, 65 (1923); see *McClain* v. *Ortmayer*, 141 U.S. 419, 424 (1891) (claims "apprise the public of what is still open to them").

Enzo further argues that claims need not be *that* precise—merely "'sufficiently definite to guide those skilled in the art to its successful application.'" BIO 1, 13 (quoting *Minerals Separation* v. *Hyde*, 242 U.S. 261, 271 (1916)). But *Minerals Separation* did not overturn this Court's numerous precedents requiring precision and clarity, nor has any decision so understood it. To the extent there were tension between *Minerals Separation* and those other decisions, that would be more reason to grant the petition, not less. Enzo similarly justifies ambiguous claiming on the theory that some uncertainty already is created by the doctrine of equivalents. BIO 16-17, 20-21. This

---

[2] That claim language may be interpreted in light of other parts of the patent, BIO 21, is not in dispute. *See Phillips* v. *AWH Corp.* 415 F.3d 1303, 1316-19 (Fed. Cir. 2005) (en banc). Nor has Applera ever argued that *any* ambiguity in claim construction gives rise to indefiniteness. BIO 16.

has matters backwards. It is precisely because of the potential for such uncertainty that that doctrine has been carefully circumscribed. *Warner-Jenkinson* v. *Hilton Davis Chem.*, 520 U.S. 17, 29 (1997). It also is why cases arising under that doctrine contain some of this Court's strongest statements about the need for clear claims. Pet. 17; *Festo*, 535 U.S. at 730-32 ("The [patent] monopoly is a property right; and like any property right, its boundaries should be clear."); *Warner-Jenkinson*, 520 U.S. at 29.

2. Next, Enzo argues, certiorari should be denied because this Court has not forbidden the use of terms of degree like "substantially." BIO 1-2, 25. And, it notes, words of degree commonly are used. *Id.* at 1-2, 12-14. This is the reddest of red herrings. Nowhere has Applera argued that words of degree are indefinite per se. Rather, they can lend themselves to indefiniteness when, as here, they are not clearly defined. *Eibel Process*, upon which Enzo repeatedly relies, held the terms "high" and "substantial" definite only because the description of the invention was sufficiently specific to permit the public to discern "how the discovery ... can be made and how its infringement could be avoided." 261 U.S. at 65. *United Carbon*, decided after *Eibel*, held that claims employing the term "substantially" were indefinite because the invention was not "accurately defined." 317 U.S. at 237. Nothing in the petition advocates or would require that *Eibel Process* be "overturn[ed]." BIO 26.

Notably, Enzo is forced to acknowledge that the three other cases it relies on to defend terms of degree did not even address indefiniteness. BIO 15 n.3. Rather, Enzo says, if those claim terms were indefinite, this Court would have said so sua sponte. That, of course, is directly contrary to this Court's usual practice.

3. Enzo all but ignores the state of the law in the Federal Circuit. Enzo does not dispute that the "capable of construction" test is circuit law. Pet. 19 (citing cases). It does not address or defend the Federal Circuit cases, discussed in the petition, which employ that test. *Compare* Pet. 18-19, *with* BIO v-viii. It does not dispute that, in evaluating whether a claim is "capable of construction," the Federal Circuit commonly asks whether a claim is "insolubly ambiguous." Pet. 19 (citing cases). Perhaps most telling, Enzo never even argues that the Federal Circuit's test is consistent with the statutory language or this Court's interpretation of it.

Instead, Enzo observes, the Federal Circuit did not recite the words "insolubly ambiguous" here. BIO 2, 13-14. But the Federal Circuit undisputedly employed the "capable of construction" test, see Pet. 11, 26; Pet. App. 10a, of which the "insolubly ambiguous" formulation is part. Enzo suggests that the decision below employed a less objectionable test—whether "'those skilled in the art would understand what is claimed.'" BIO 10, 13 (quoting Pet. App. 11a). But the panel quoted that language from *Young* v. *Lumenis*, which holds that claims are indefinite only when they are "'not amenable to construction or are insolubly ambiguous,'" 492 F.3d 1336, 1346 (Fed. Cir. 2007); and it relied on *Datamize, LLC* v. *Plumtree Software*, which holds likewise, 417 F.3d 1342, 1347-48 (Fed. Cir. 2005). Pet. App. 11a. Like the panel's determination that claims are definite when they provide merely "some guidance," Pet. App. 14a, *Young* likewise found claims definite because they could "'be given any reasonable meaning.'" 492 F.3d at 1346. Neither formulation is remotely consistent with the "particular[ity] and distinct[ness]" required by the statute.

Enzo elsewhere argues that definiteness remains a "powerful tool" in the Federal Circuit. BIO 27. Its flimsy examples prove the opposite. *Quantum Corporation* v. *Rodime* did not address indefiniteness at all, but rather considered whether the claims were impermissibly broadened during reexamination. 65 F.3d 1577, 1580 (Fed. Cir. 1995). *Acacia Media Technologies Corporation* v. *New Destiny Internet Group* is one unpublished decision by one district court, which was affirmed in an unpublished order by the Federal Circuit. See BIO 27. By contrast, a recent study of Federal Circuit decisions confirms that, when the issue is breadth of terminology (rather than a technical defect), claims rarely are held indefinite. Altera Br. 11 & n.3. Enzo quibbles about the precise figures in the article (BIO 27), but cannot identify a single Federal Circuit decision that employs the definiteness doctrine in a meaningful fashion.

That is why it is necessary for this court to intervene. As Enzo itself acknowledges, "[f]or a decade, the Federal Circuit has employed its current standards without meaningful dispute or dissent." BIO 25. Judge Plager may not be an "active judge," *id.* at 3, 17, but he is experienced and has accurately explained the serious problem in the Federal Circuit's jurisprudence, and no other judge on that court will take action. As in *KSR International* v. *Teleflex*, 550 U.S. 398, 412-14 (2007)—where the Federal Circuit adopted an atextual invalidity test, and *no* Federal Circuit judge (active or senior) voiced dissent—review by this Court is the only option to restore definiteness to its moorings.

The erroneous Federal Circuit test is of abiding importance to the proper application of the patent laws. The requirement of definiteness applies to every claim in every patent, and a feckless indefiniteness

test creates perverse incentives for drafting overly broad claims, to the detriment of the public. See Pet. 17-18; S. Jay Plager, *The Federal Circuit As An Institution: Of Uncertainty and Policy Levers*, 43 Loyola L.A. L. Rev. 749, 758-59 (2010). As the FTC recognized in its seminal 2003 report, "questionable patents are a significant competitive concern and can harm innovation." *To Promote Innovation: The Proper Balance Of Competition and Patent Law and Policy*, exec. summ. 5 (2003) (capitalization omitted). Companies avoid researching in or entering fields covered by such questionable patents, and engage in defensive patenting. *Id.* at 5-7. As the array of *amicus* corporations supporting the petition explain, such patents incentivize litigation by patent trolls, leaving companies vulnerable to coercive and expensive settlements. Yahoo Br. 13-14; Altera Br. 15-16. That Yale itself is not a troll, BIO 27 n.8, is irrelevant; this issue is important because patent trolls can and do exploit the uncertainty caused by the Federal Circuit's test.

II. THE FEDERAL CIRCUIT'S INTERPRETATION OF § 112 CONFLICTS WITH THE PTO'S.

The Federal Circuit and the PTO employ different tests for definiteness. Pet. 23-26. Enzo does not dispute this; it responds that this approach is justified by the difference between pre-issuance and post-issuance review. BIO 22. But the petition itself notes this justification, as did the PTO in *Ex parte Miyazaki*. Pet. 24. The question is whether the differing standards can be squared with the fact that both the PTO and the Federal Circuit are applying the same statutory text. Enzo contends that an applicant can amend its claims to "'more clearly and precisely define'" the invention's boundaries only be-

fore the patent issues. BIO 22. On the contrary, defects in already-issued claims can be cured through reexamination, or through the reissue process of 35 U.S.C. § 251, see *Keystone Bridge* v. *Phoenix Iron*, 95 U.S. 274, 278-79 (1877); *Merrill* v. *Yeomans*, 94 U.S. 568, 573 (1876).[3] More to the point, whatever the BPAI's rationalization for differing standards, the United States seems to question the Federal Circuit test—as evidenced by the brief it filed on rehearing en banc in *Ariad*. Pet. 25. On this point, Enzo offers no response. At a bare minimum, therefore, the Court should seek the views of the United States.

Finally, Enzo asserts that there is no conflict because the PTO and the Federal Circuit both concluded here that the claims were definite. BIO 24-25, 29. But the PTO allowed the claims at least a decade before the BPAI decided *Miyazaki*. BIO App. 1a.

III. THE DECISION BELOW IS AN EXCELLENT VEHICLE FOR RESOLVING THESE ISSUES.

The gross ambiguity of Enzo's patents makes this case a particularly good vehicle for addressing the important question presented. Pet. 26-29. For the Federal Circuit, the claims were definite because of mere examples in the specification and dependent claims. Pet. App. 17a (one can perform tests to "see whether they fall within the range of exemplary values disclosed"). Those examples, however, do not demarcate a floor or ceiling for what the claims

---

[3] Enzo also argues that the PTO and the Federal Circuit apply different standards in certain contexts. BIO 23-24. But the examples it cites principally concern burdens of proof rather than substantive tests, for which the PTO and Federal Circuit otherwise do use the same tests, Pet. 24 n.10, and it offers no other example where they interpret the statute differently.

purport to cover. Pet. 26-27. Importantly, Enzo does not contend otherwise. Cf. BIO 14.

Instead, Enzo disparages Applera's indefiniteness argument as a request that Enzo's patent "tell [Applera] how to build around [the patent] by making a molecule that would not work." BIO 31; *id.* at 4. On Enzo's theory, the "claims would cover any interactions which succeed, but not those which do not—rendering 'substantial' a nullity." Pet. App. 58a.[4] It is Enzo's job to tell the public what it thinks would "work." This case illustrates why that is important: The linkage group used by Applera interferes somewhat with hybridization—just not so much as to prevent it entirely—and indeed some interference is affirmatively helpful to the Applera system. Defendants' Opposition at 12, No. 04-CV-929 (D. Conn. Mar. 26, 2007) (Dkt. 216). It therefore is critical to know the bounds of what Enzo thinks "work[s]." Any other approach is profoundly anticompetitive and harmful to consumers.

---

[4] Elsewhere, however, Enzo suggests that its patents do *not* contain functional claims, but rather specify "concrete chemical structure." BIO 30. This is simply incorrect. The patent discloses a generic structural configuration, but (as the Federal Circuit recognized) the linkage group at issue here is recited in functional terms. Pet. App. 4a; Pet. 9-10 & n.6. The letter to the PTO cited by Enzo says nothing about the linkage group, its structure, or the limits thereof. BIO 30 (citing BIO App. 51a).

Enzo asserts in passing that Applera has waived any argument about functional claim language. BIO 29-30 & n.11. The functional nature of the claim language is not, however, a separate, waivable issue. This Court repeatedly has warned about the potential overbreadth of functional claims, *see* Pet. 27 & n.12, and here the indefiniteness problem is exacerbated because the word of degree appears within functional claim language. Applera has so argued throughout. *E.g.*, CAFC Red Br. 32-35.

Finally, Enzo notes that this case is interlocutory. BIO 31-32. But that is no obstacle to review "where the opinion of the court below has decided an important issue, otherwise worthy of review, and Supreme Court intervention may serve to hasten or finally resolve the litigation." Eugene Gressman et al., *Supreme Court Practice* 282 (9th ed. 2007) (citing cases). Indefiniteness is an issue of law reviewed de novo, see Pet. App. 9a; it has been finally adjudicated; and, if reversed, it will resolve this litigation. Further proceedings on remand would not assist this Court's review. The Court has reviewed patent cases in the same posture. *E.g.*, *KSR*, 550 U.S. at 412-14 (reviewing decision reversing summary judgment of invalidity).

CONCLUSION

For the foregoing reasons and those in the petition, the petition for a writ of certiorari should be granted.

Respectfully submitted,

NICHOLAS GROOMBRIDGE
JENNIFER H. WU
WEIL, GOTSHAL & MANGES LLP
767 Fifth Avenue
New York, NY 10153
(212) 310-8000

ANTON J. BOKAL
ALAN W. HAMMOND
KURTIS D. MACFERRIN
LIFE TECHNOLOGIES CORP.
850 Lincoln Centre Dr.
Foster City, CA 94404
(650) 554-3410

CARTER G. PHILLIPS*
ERIC A. SHUMSKY
RACHEL TOWNSEND
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, DC 20005
(202) 736-8000
cphillips@sidley.com

TACY F. FLINT
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, IL 60603
(312) 853-7000

JOHN M. WHEALAN
12 Sunnyside Road
Silver Spring, MD 20910
(202) 994-2195

Counsel for Petitioner

November 22, 2010

*Counsel of Record

(10)

No. 10-426

In the Supreme Court of the United States

APPLERA CORP., ET AL., PETITIONERS

v.

ENZO BIOCHEM, INC., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

NEAL KUMAR KATYAL
Acting Solicitor General
Counsel of Record

TONY WEST
Assistant Attorney General

MALCOLM L. STEWART
Deputy Solicitor General

SARAH E. HARRINGTON
Assistant to the Solicitor General

SCOTT R. MCINTOSH
MARK R. FREEMAN
Attorneys

Department of Justice
Washington, D.C. 20530-0001
SupremeCtBriefs@usdoj.gov
(202) 514-2217

BERNARD J. KNIGHT, JR.
General Counsel

RAYMOND T. CHEN
Solicitor and Deputy General Counsel

NATHAN K. KELLEY
KRISTI L.R. SAWERT
AMY J. NELSON
Associate Solicitors
U.S. Patent and Trademark Office
Alexandria, Va. 22313

QUESTION PRESENTED

Whether respondents' patent claims satisfy the requirement of Section 112 of the Patent Act, 35 U.S.C. 112, that the specification of a patent "shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

TABLE OF CONTENTS

Page

Statement 1
Discussion 6
A. The court of appeals correctly held that a patent claim is sufficiently definite if a person skilled in the relevant art would understand what is being claimed 7
B. There is no conflict warranting this Court's intervention 11
C. The court of appeals' decision is correct 18
Conclusion 22

TABLE OF AUTHORITIES

Cases:

Amgen, Inc. v. *Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991) 12
Bancorp Servs., L.L.C. v. *Hartford Life Ins. Co.*, 359 F.3d 1367 (Fed. Cir. 2004) 13
Barber v. *Thomas*, 130 S.Ct. 2499 (2010) 14
Carnegie Steel Co. v. *Cambria Iron Co.*, 185 U.S. 403 (1902) 2, 9
Eibel Process Co. v. *Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923) 10, 11, 21
Evans v. *Eaton*, 20 U.S. (7 Wheat.) 356 (1822) 7
Exhibit Supply Co. v. *Ace Patents Corp.*, 315 U.S. 126 (1942) 9
Exxon Research & Eng'g Co. v. *United States*, 265 F.3d 1371 (Fed. Cir. 2001) 13, 18
Festo Corp. v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002) 2, 7, 8, 9, 10

Cases—Continued: Page

General Elec. Co. v. *Wabash Appliance Corp.*, 304 U.S. 364 (1938) 8
Haemonetics Corp. v. *Baxter Healthcare Corp.*, 607 F.3d 776 (Fed. Cir. 2010) 14
Halliburton Energy Servs., Inc. v. *M-I LLC*, 514 F.3d 1244 (Fed. Cir. 2008) 12, 13, 14, 17
Hogg v. *Emerson*, 52 U.S. 587 (1850) 9
Keystone Bridge Co. v. *Phoenix Iron Co.*, 95 U.S. 274 (1877) 8
Markman v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996) 2, 4, 7, 9, 14
Marosi, In re, 710 F.2d 799 (Fed. Cir. 1983) 19
McClain v. *Ortmayer*, 141 U.S. 419 (1891) 2, 8, 22
Merrill v. *Yeomans*, 94 U.S. 568 (1876) 7
Minerals Separation, Ltd. v. *Hyde*, 242 U.S. 261 (1916) 9, 10, 21
Miyazaki, Ex parte, No. 2007-3300, 2008 WL 5105055 (Bd. Pat. App. & Inter. Nov. 19, 2008) 17
Morris, In re, 127 F.3d 1048 (Fed. Cir. 1997) 18
Muscarello v. *United States*, 524 U.S. 125 (1988) 14
Orthokinetics, Inc. v. *Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1986) 12
Permutit Co. v. *Graver Corp.*, 284 U.S. 52 (1931) 8
Personalized Media Commc'ns, LLC v. *ITC*, 161 F.3d 696 (Fed. Cir. 1998) 12
Phillips v. *AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), cert. denied, 546 U.S. 1170 (2006) 12
Schriber-Schroth Co. v. *Cleveland Trust Co.*, 311 U.S. 211 (1940) 9

Cases—Continued: Page

Shatterproof Glass Corp. v. *Libbey-Owens Ford Co.*, 758 F.2d 613 (Fed. Cir.), cert. dismissed, 474 U.S. 976 (1985) 12

Smith v. *Snow*, 294 U.S. 1 (1935) 22

Star Scientific, Inc. v. *R.J. Reynolds Tobacco Co.*, 537 F.3d 1357 (Fed. Cir. 2008) 13, 14

United Carbon Co. v. *Binney & Smith Co.*, 317 U.S. 228 (1942) 8

United States v. *Adams*, 383 U.S. 39 (1966) 9

Young v. *Lumenis, Inc.*, 492 F.3d 1336 (Fed. Cir. 2007) 5, 11

Statutes:

Act of Apr. 10, 1790, ch. 7, § 2, 1 Stat. 110-111 7

Act of Feb. 21, 1793, ch. 11, § 3, 1 Stat. 321-322 7

Act of July 8, 1870, ch. 230, § 26, 16 Stat. 201 7

35 U.S.C. 102 ..... 4, 16

35 U.S.C. 111 1

35 U.S.C. 112 ..... *passim*

35 U.S.C. 282 18

35 U.S.C. 282(3) 2

Miscellaneous:

Supplementary Examination Guidelines for Determining Compliance With 35 U.S.C. 112 and for Treatment of Related Issues in Patent Applications, 76 Fed. Reg. 7162 (2011) 2, 6

p. 7164 ..... 17, 18, 21

Miscellaneous—Continued: Page

U.S. Patent & Trademark Office, *Manual of Patent Examining Procedure* (rev. ed. 2010) 17

In the Supreme Court of the United States

No. 10-426

APPLERA CORP., ET AL., PETITIONERS

v.

ENZO BIOCHEM, INC., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

This brief is filed in response to the Court's order inviting the Acting Solicitor General to express the views of the United States. In the view of the United States, the petition for a writ of certiorari should be denied.

STATEMENT

1. Each written application for a patent must include "a specification as prescribed by section 112" of the Patent Act. 35 U.S.C. 111. The specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains * * * to make and use the same." 35 U.S.C. 112, ¶ 1. "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter

which the applicant regards as his invention." 35 U.S.C. 112, ¶ 2.

The last of those provisions imposes what is known in patent parlance as the "definiteness" requirement: each patent must conclude with specific "claims" that, when construed in light of the specification and the relevant prosecution history, communicate to persons skilled in the art the legal scope of the patent grant. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996); *Carnegie Steel Co.* v. *Cambria Iron Co.*, 185 U.S. 403, 432, 437 (1902); see generally *Supplementary Examination Guidelines for Determining Compliance With 35 U.S.C. 112 and for Treatment of Related Issues in Patent Applications*, 76 Fed. Reg. 7162 (2011) (*PTO Definiteness Guidelines*). Compliance with Section 112 serves the dual purposes of "secur[ing] to [the patentee] all to which he is entitled, [and] appris[ing] the public of what is still open to them." *Markman*, 517 U.S. at 373 (quoting *McClain* v. *Ortmayer*, 141 U.S. 419, 424 (1891)) (second set of brackets in original); see *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002). An inventor's failure to comply with any requirement of Section 112 renders the patent or claim in suit invalid. See 35 U.S.C. 282(3).

2. a. The patents at issue in this case concern laboratory techniques for detecting nucleic acids—such as deoxyribonucleic acid (DNA)—in a test sample. Pet. App. 2a. The basic structure of DNA includes two strands of repeating chemical units, known as "nucleotides" or "bases," bound together like a zipper and twisted into a distinctive double helix. The four standard nucleotides—adenine (A), thymine (T), cytosine (C), and guanine (G)—are chemically paired such that cytosine

always binds (or "hybridizes") with guanine, and adenine with thymine. *Id.* at 2a-3a.

Because of the predictable way in which nucleotides pair to form the "teeth" of the zipper, it is possible to infer from a nucleotide sequence on one strand of DNA the corresponding nucleotide sequence on the strand with which it may hybridize. Pet. App. 3a. Scientists may therefore detect whether a specific nucleotide sequence on a strand of DNA—for example, the sequence associated with a particular genetic condition—is present in a test sample. *Ibid.* Scientists attach a readily detected chemical entity (a "label") to a nucleic acid strand of a known sequence (a "probe") that will hybridize with the complementary sequence of interest (the "target"). *Ibid.* Copies of the labeled probe are then introduced into a test sample containing DNA strands of unknown sequence under conditions that permit the probe to hybridize with the target nucleic acid, if present. *Ibid.* After removing any unhybridized probes, scientists look for evidence that the label remains in the sample. Detection of the label implies that a probe has successfully hybridized, which in turn implies that the target nucleic acid is present. *Ibid.*; see *id.* at 80a-81a.

b. Although the use of labeled probes to detect nucleic acids has long been known in the art, previous detection methods generally involved the use of radioactive labels, which can be expensive, unstable, and hazardous. See Pet. App. 3a-4a. The patents at issue in this case are directed to nucleic acid detection probes and related methods that do not require the use of radioactive labels. Respondents are assignees of the relevant patents, U.S. Patents No. 5,328,824 (the '824 patent), No. 5,449,767 (the '767 patent), No. 5,476,928 (the '928 patent), and No. 5,082,830 (the '830 patent). *Id.* at 4a.

Those patents describe the use of a new type of label consisting of a chemical moiety that is covalently bonded to the probe either directly or through a "linkage group." *Ibid.* The linkage group is a chemical structure designed to hold the signaling moiety (the label) physically away from the probe to prevent it from interfering with either the probe's ability to hybridize with the target nucleic acid or the label's ability to be detected after hybridization is complete. *Id.* at 4a-6a. In effect, the patents teach that a successfully hybridized probe can be made detectable by attaching to the probe a kind of chemical flagpole with a distinctive chemical flag on the end, rather than by using radioactive isotopes.

The claims of the '824, '767, and '928 patents specifically recite the chemical structure of the claimed probe. See Pet. App. 4a-6a. The claims also indicate the range of covered labels, both by describing their chemical structure and by reciting examples of acceptable labels. See *id.* at 5a-6a. The linkage group (*i.e.*, the flagpole), however, is described in functional rather than structural terms: it is identified by its essential characteristic of "not interfering substantially" with the probe's ability to hybridize with the target or with the label's ability to be detected. *Id.* at 4a-5a.

3. In June 2004, respondents sued petitioners for patent infringement. Pet. App. 6a. After the district court construed the asserted patent claims, cf. *Markman*, 517 U.S. at 372, respondents conceded noninfringement of the '830 patent. Pet. App. 7a-8a. Petitioners then moved for summary judgment of invalidity of all asserted claims of the '824, '767, and '928 patents, arguing that those claims were anticipated under 35 U.S.C. 102 and that they failed to comply with the writ-

ten description, enablement, and definiteness requirements of 35 U.S.C. 112. Pet. App. 8a.

The district court granted the motion and declared all of the asserted claims invalid. See Pet. App. 34a-73a. The court concluded that each claim was anticipated by published scientific articles in the prior art. *Id.* at 8a & n.3, 61a-73a. The court also held that the asserted claims were invalid because the "not interfering substantially" language rendered the scope of the claims indefinite. *Id.* at 8a, 51a-61a. The court concluded that the "specifications neither set forth how one would gauge substantial interference, nor delimit the threshold at which interference with the procedure prevents [the] method from being implemented." *Id.* at 60a.

4. The court of appeals reversed in part, affirmed in part, and remanded. Pet. App. 1a-33a.

The court of appeals reversed the district court's finding of indefiniteness. Pet. App. 10a-19a. The court explained that the relevant inquiry was "whether those skilled in the art would understand what is claimed" in light of "the claim language, the specification, and the prosecution history." *Id.* at 11a (quoting *Young* v. *Lumenis, Inc.*, 492 F.3d 1336, 1346 (Fed. Cir. 2007)). Applying that standard, the court concluded that the term "substantially interfere," as used in the claims, was sufficiently definite because the claims, specification, and prosecution history provide not only general instructions for selecting linkage groups that satisfy the claims, but also specific examples of acceptable linkage groups identified by chemical structure. See *id.* at 12a-19a. The court held that the asserted claims are not indefinite because a person skilled in the art can deter-

mine whether a particular linkage group falls within the scope of the claims. *Id.* at 16a-17a.[1]

The court of appeals reversed the district court's summary judgment ruling that the '824 and '767 patents are invalid as anticipated by the prior art, but it affirmed the finding of invalidity as to the '928 patent. Pet. App. 19a-27a. The court also affirmed the judgment of noninfringement as to the '830 patent. *Id.* at 27a-32a.

5. Petitioners filed a petition for panel rehearing and rehearing en banc, which was denied. Pet. App. 74a-75a. Senior Judge Plager dissented from the denial of panel rehearing, urging that the Federal Circuit's "definiteness doctrine could go considerably further in promoting" the public notice function of patent claims under Section 112. *Id.* at 78a.

DISCUSSION

The court of appeals correctly held that Section 112's definiteness requirement was satisfied here because a person with ordinary skill in the art of designing probes for nucleic acid detection would reasonably understand the scope of the asserted patent claims in light of the specification and the prosecution history of the patents. That approach is consistent with this Court's precedents. It is also consistent with the views of the Patent and Trademark Office (PTO), which the agency recently restated in formal guidelines to assist examiners in applying the definiteness requirement. See generally *PTO Definiteness Guidelines*, 76 Fed. Reg. 7162 (2011). This Court's review is not warranted.

---

[1] "[F]or most of the same reasons," the court held that the requirement that the linkage group not substantially interfere with detection of the signaling moiety likewise was not indefinite. Pet. App. 18a-19a.

A. The Court Of Appeals Correctly Held That A Patent Claim Is Sufficiently Definite If A Person Skilled In The Relevant Art Would Understand What Is Being Claimed

1. Section 112 promotes the "delicate balance the law attempts to maintain between inventors, who rely on the promise of the law to bring the invention forth, and the public, which should be encouraged to pursue innovations, creations, and new ideas beyond the inventor's exclusive rights." *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002). Although the practice of appending formal "claims" to the written specification of a patent did not achieve statutory recognition until 1836 and was not statutorily required until 1870, see *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 379 (1996), the Patent Act has provided since 1790 that a patent applicant must both (a) describe his claimed invention with sufficient clarity to enable a person skilled in the art to make or use the invention and (b) distinguish the invention from the prior art. See, *e.g.*, Act of Apr. 10, 1790, ch. 7, § 2, 1 Stat. 110-111; Act of Feb. 21, 1793, ch. 11, § 3, 1 Stat. 321-322; *Evans* v. *Eaton*, 20 U.S. (7 Wheat.) 356, 433-434 (1822).

In 1870, Congress enacted the first explicit requirement that, as part of the written specification, a patent applicant must "particularly point out and distinctly claim the part, improvement, or combination which he claims as his invention or discovery." Act of July 8, 1870, ch. 230, § 26, 16 Stat. 201; see *Markman*, 517 U.S. at 379. That 1870 amendment assisted courts in ascertaining what an inventor claimed as his contribution to the art by "very wisely requir[ing] of the applicant a distinct and specific statement of what he claims to be new, and to be his invention." *Merrill* v. *Yeomans*, 94

U.S. 568, 570 (1876); see *Keystone Bridge Co.* v. *Phoenix Iron Co.*, 95 U.S. 274, 278 (1877). The inclusion of such claims in the specification also served to "apprise the public of what is still open to them." *McClain* v. *Ortmayer*, 141 U.S. 419, 424 (1891).

2. a. As petitioners observe (Pet. 16-18), this Court has repeatedly emphasized the importance of the notice function of patent claims. See, *e.g.*, *General Elec. Co.* v. *Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938); *Permutit Co.* v. *Graver Corp.*, 284 U.S. 52, 60 (1931). As the Court explained in *United Carbon Co.* v. *Binney & Smith Co.*, 317 U.S. 228, 236 (1942), "[a] zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field." By requiring that patent claims provide clear notice of the metes and bounds of the patented invention, Section 112 reduces such uncertainty.

This Court has recognized, however, that it is often impossible to reduce an invention—including every embodiment and application to which it may extend—to writing with faultless precision and clarity. "Unfortunately, the nature of language makes it impossible to capture the essence of a thing in a patent application." *Festo*, 535 U.S. at 731. The fact that a court must interpret claim language in order to resolve questions of infringement does not mean that the language is fatally indefinite.

b. This Court has announced various principles governing the construction of disputed patent claims. First, claim language should be viewed not from the perspective of the public at large, but from the perspective of other persons "skilled in the art to which [the invention] pertains, or with which it is most nearly connected." 35

U.S.C. 112, ¶ 1. Thus, in discussing a patent for an improved method of manufacturing steel, the Court explained that "[t]he specification of the patent is not addressed to lawyers, or even to the public generally, but to the manufacturers of steel, and any description which is sufficient to apprise them in the language of the art of the definite feature of the invention, and to serve as a warning to others of what the patent claims as a monopoly, is sufficiently definite to sustain the patent." *Carnegie Steel Co.* v. *Cambria Iron Co.*, 185 U.S. 403, 437 (1902); see *Minerals Separation, Ltd.* v. *Hyde*, 242 U.S. 261, 271 (1916).

Second, patent claims should be interpreted in light of the patent's written specification rather than in isolation. See, *e.g.*, *Markman*, 517 U.S. at 389-390; *United States* v. *Adams*, 383 U.S. 39, 49 (1966); *Carnegie Steel*, 185 U.S. at 432; *Hogg* v. *Emerson*, 52 U.S. 587, 606 (1850). Third, "the prosecution history [of a patent] is relevant to construing [its] claims." *Festo*, 535 U.S. at 741; see *Exhibit Supply Co.* v. *Ace Patents Corp.*, 315 U.S. 126, 136-137 (1942); *Schriber-Schroth Co.* v. *Cleveland Trust Co.*, 311 U.S. 211, 217-218, 220-221 (1940). In *Festo*, the Court held that amendments made during prosecution to overcome an examiner's objections under 35 U.S.C. 112 become part of the interpretive background of the allowed claims and may give rise to estoppel in litigation. See 535 U.S. at 736-737.

c. This Court's decisions make clear that a patent claim can be sufficiently definite to satisfy Section 112 even if its language requires some interpretation against the backdrop of the relevant art, the patent specification, and the prosecution history. The Court has repeatedly declined to endorse the strongest form of the argument that petitioners advance here—*i.e.*, that patent

claims must "provide the public with *certainty* * * * about the scope of [the] patent." Pet. 21 (emphasis added). For example, the Court has recognized a "doctrine of equivalents" under which the "scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims described." *Festo*, 535 U.S. at 732. Such a doctrine is necessary, the Court has explained, because "[t]he language in the patent claims may not capture every nuance of the invention or describe with complete precision the range of its novelty." *Id.* at 731. While recognizing "that the doctrine of equivalents renders the scope of patents less certain," this Court has long viewed "this uncertainty as the price of ensuring the appropriate incentives for innovation." *Id.* at 732. More generally, the Court has explained that "the certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter." *Minerals Separation*, 242 U.S. at 270.

A claim may be sufficiently definite under Section 112 even though it employs terms of degree in order to allow for some variation in the method of applying the invention at issue. For example, the patent in *Minerals Separation* involved an improved process for extracting valuable minerals from crushed ore. The Court rejected the accused infringer's contention that the process was not claimed with sufficient precision because aspects of the process had to be varied, through experimentation, to achieve the best results with different types of ore. 242 U.S. at 270. Similarly, in *Eibel Process Co.* v. *Minnesota & Ontario Paper Co.*, 261 U.S. 45, 66 (1923), the Court upheld against an indefiniteness challenge a patent directed to a machine for manufacturing paper stock that used gravity to improve the speed of the output by starting the paper-making wire at a "high" or "substan-

tial elevation above the level." *Id.* at 50. The Court explained that it was "difficult" for the patentee to be "more definite, due to the varying conditions of speed and stock existing in the operations of [such] machines and the necessary variation in the pitch to be used to accomplish the purpose of his invention." *Id.* at 65. A person skilled in the art of using such machines, the Court continued, would have "no difficulty * * * in determining what was the substantial pitch needed" to obtain the benefit of the invention. *Id.* at 65-66.

3. The ruling below reflects a sound understanding of the principles announced in this Court's decisions. The court of appeals explained that an allegation of "[i]ndefiniteness requires a determination whether those skilled in the art would understand what is claimed" in light of "general principles of claim construction." Pet. App. 11a (quoting *Young* v. *Lumenis, Inc.*, 492 F.3d 1336, 1346 (Fed. Cir. 2007)). The court further noted that "claim construction involves consideration of primarily the intrinsic evidence, *viz.*, the claim language, the specification, and the prosecution history." *Ibid.* The court also rejected petitioners' argument that the claims were indefinite because the choice of a linkage group might vary depending on the length and sequence of the relevant DNA strand. *Id.* at 17a-18a. The court's application of the standard imposed by Section 112 is faithful both to the language of the statute and to this Court's interpretation of that language.

B. There Is No Conflict Warranting This Court's Intervention

Petitioners assert (Pet. 16-22) that the Federal Circuit's definiteness standard is inconsistent with the language of Section 112 and with this Court's decisions.

While the Federal Circuit has sometimes used imprecise language to describe the definiteness standard, the court has generally adhered to the principles articulated by this Court. Petitioners are also wrong in contending (Pet. 23-26) that the Federal Circuit's jurisprudence impermissibly conflicts with the PTO's approach to resolving issues of definiteness during the examination process. Rather, the difference between the two entities' approaches is attributable to the distinct roles that the PTO and the Federal Circuit perform.

1. a. In applying the definiteness requirement of Section 112, the Federal Circuit has repeatedly stated that claims must be understood from the perspective of a person skilled in the relevant art and must be construed in light of the patent's specification and prosecution history. See, *e.g.*, *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1312-1313 (2005) (en banc), cert. denied, 546 U.S. 1170 (2006). Although a particular claim may "present a difficult task of claim construction," such a claim is invalid as indefinite only if "a skilled artisan could not discern the boundaries of the claim based on the claim language, the specification, and the prosecution history, as well as her knowledge of the relevant art area." *Halliburton Energy Servs., Inc.* v. *M-I LLC*, 514 F.3d 1244, 1249-1250 (Fed. Cir. 2008) (*Halliburton*). The Federal Circuit has applied some version of that standard to resolve indefiniteness issues for nearly the entire period that the court has been in existence. See, *e.g.*, *Shatterproof Glass Corp.* v. *Libbey-Owens Ford Co.*, 758 F.2d 613, 624 (Fed. Cir.), cert. dismissed, 474 U.S. 976 (1985); *Orthokinetics, Inc.* v. *Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986); *Amgen, Inc.* v. *Chugai Pharm. Co.*, 927 F.2d 1200, 1217 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); *Personalized Media*

Commc'ns, LLC v. *ITC*, 161 F.3d 696, 705 (Fed. Cir. 1998). As petitioners acknowledged in their rehearing petition in the court of appeals (at 6), those decisions correctly articulate Section 112's definiteness standard as interpreted by this Court.

b. In arguing that the Federal Circuit's standard for definiteness is inconsistent with the text of Section 112 and with this Court's precedents, petitioners focus primarily (*e.g.*, Pet. 19) on Federal Circuit opinions stating that patent claims are sufficiently definite if they are "capable of construction" and not "insolubly ambiguous." Read in isolation, those phrases might suggest an insufficiently demanding definiteness standard to a district court looking for guidance. At least in the main run of its decisions, however, the Federal Circuit has used those phrases to express principles that are well grounded in this Court's Section 112 jurisprudence.

The Federal Circuit has most frequently used the relevant phrases to express the insight that a patent claim may be sufficiently definite to satisfy Section 112 even though considerable study and analysis are required to discern its meaning. See, *e.g.*, *Bancorp Servs., L.L.C.* v. *Hartford Life Ins. Co.*, 359 F.3d 1367, 1371 (2004) ("[A] claim is not indefinite merely because it poses a difficult issue of claim construction; if the claim is subject to construction, i.e., it is not insolubly ambiguous, it is not invalid for indefiniteness."); *Star Scientific, Inc.* v. *R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1371 (2008); *Halliburton*, 514 F.3d at 1249; *Exxon Research & Eng'g Co.* v. *United States*, 265 F.3d 1371, 1375 (2001) (*Exxon*). The proposition that substantial effort may be required to construe even a "definite" claim is not open to serious dispute. Because individual claims are construed in light of the patent as a whole, and because the

definiteness inquiry focuses on the claim's comprehensibility to a person skilled in the art (rather than to a generalist judge who may initially lack relevant technical expertise), a claim may satisfy Section 112 even though an arduous inquiry is required to ascertain its meaning. Cf. *Markman*, 517 U.S. at 387, 389 (explaining that trial court's construction of a patent claim may be informed by expert testimony concerning the relevant art, and that claim construction requires a "necessarily sophisticated analysis of the whole document").[2] Insofar as phrases like "insolubly ambiguous" function as shorthand references to those principles, they are fully consistent with this Court's precedents.

The contexts in which the Federal Circuit has used phrases like "insolubly ambiguous" and "open to construction" indicate that the court views those tests as synonymous with (or at least complementary to) the inquiry whether the relevant claim is understandable to one skilled in the art. See, *e.g.*, *Haemonetics Corp.* v. *Baxter Healthcare Corp.*, 607 F.3d 776, 783 (2010) (identifying "not amenable to construction" and "insolubly ambiguous" as the governing standards, and then stating that a party asserting indefiniteness must show "that one of ordinary skill in the relevant art could not discern the boundaries of the claim"); *Halliburton*, 514 F.3d at 1249 ("[C]laims [are] held indefinite only where a person of ordinary skill in the art could not determine the bounds of the claims, i.e., the claims [are] insolubly ambiguous."); *Star Scientific*, 537 F.3d at 1371 ("[I]f

---

[2] Cf. *Barber* v. *Thomas*, 130 S. Ct. 2499, 2508 (2010) ("[T]he rule of lenity only applies if, after considering text, structure, history, and purpose, there remains a 'grievous ambiguity or uncertainty in the statute.'") (quoting *Muscarello* v. *United States*, 524 U.S. 125, 139 (1998)).

reasonable efforts at claim construction result in a definition that does not provide sufficient particularity and clarity to inform skilled artisans of the bounds of the claim, the claim is insolubly ambiguous and invalid for indefiniteness."). To be sure, any legal standard is capable of misapplication in particular cases, and the Federal Circuit may on occasion have used phrases like "insolubly ambiguous" and "capable of construction" while conducting a definiteness inquiry that in substance was insufficiently rigorous. But given the frequency and explicitness with which the Federal Circuit has linked those phrases to the principles of law announced in this Court's decisions, the court of appeals' terminology does not reflect any systematic deviation from correct application of Section 112.

c. In any event, the court of appeals did not use either the phrase "insolubly ambiguous" or the phrase "capable of construction" in its opinion below. Rather, the court explained that "[i]ndefiniteness requires a determination whether those skilled in the art would understand what is claimed," and that "general principles of claim construction apply" in resolving that question, including "consideration of primarily the intrinsic evidence, *viz.*, the claim language, the specification, and the prosecution history." Pet. App. 11a (internal citations and quotation marks omitted). The court then analyzed the intrinsic evidence concerning "substantial interference" at length and in considerable scientific detail, focusing on the meaning that particular disclosures would convey to a person skilled in the art of designing and labeling nucleic acid probes. *Id.* at 12a-19a.

Resolving the factbound (and highly technical) merits question this case presents—*i.e.*, whether petitioners' claims adequately conveyed the scope of their inventions

to persons skilled in the art of designing and labeling nucleic acid probes—would not be a prudent use of this Court's resources. And a decision by this Court remanding with instructions not to use the phrase "insolubly ambiguous" or "capable of construction" would serve no useful purpose, since the court of appeals has already decided the definiteness issue without using those phrases. This case therefore provides an unsuitable vehicle for determining whether the Federal Circuit in *other* decisions has used phra es like "insolubly ambiguous" to announce a separate, legally deficient definiteness standard, or simply as shorthand for established principles of law.

Furthermore, the interlocutory posture of the case provides an additional reason for this Court to deny review. The court of appeals affirmed the judgment of anticipation under 35 U.S.C. 102 as to one of the four patents on appeal, Pet. App. 27a; affirmed the judgment of noninfringement as to another, *id.* at 32a; and remanded for resolution of genuine issues of material fact regarding the validity of the remaining two patents under Section 102, see *id.* at 21a. The surviving claims could therefore be invalidated on remand despite the court of appeals' rejection of petitioners' indefiniteness challenge.

2. Petitioners contend (Pet. 23-26) that this Court's intervention is necessary to resolve a "conflict" between the Federal Circuit's decisions and the PTO's interpretation of Section 112, Paragraph 2. No such conflict exists. As the PTO's recently published guidelines for examiners under Paragraph 2 of Section 112 make clear, the agency conducts essentially the same definiteness inquiry that courts apply, asking whether a person skilled in the art can reasonably understand what is

claimed in light of the specification and other intrinsic evidence. See *PTO Definiteness Guidelines*, 76 Fed. Reg. at 7164; see also U.S. Patent & Trademark Office, *Manual of Patent Examining Procedure* §§ 2171, 2173.02 (rev. ed. 2010).

The PTO does instruct agency examiners to employ "a lower threshold of ambiguity when reviewing a pending claim for indefiniteness" than that used by the Federal Circuit. *Ex parte Miyazaki*, No. 2007-3300, 2008 WL 5105055, at *5 (Bd. Pat. App. & Inter. Nov. 19, 2008); see *PTO Definiteness Guidelines*, 76 Fed. Reg. at 7164. Rather than apply a limiting construction as courts do, PTO examiners will reject a claim as indefinite if, when viewed in light of the specification as understood by a person skilled in the art, the claim is amenable to two or more plausible claim constructions. *Miyazaki*, 2008 WL 5105055, at *5-*6; *PTO Definiteness Guidelines*, 76 Fed. Reg. at 7164. That difference, however, stems not from different interpretations of Section 112, but from the distinct roles that the PTO and the courts play in the patent system. As the PTO has explained, "[t]he lower threshold is applied [during patent examination] because the patent record is in development and not fixed." *Ibid.* At that point, the PTO construes patent claims broadly "in an effort to establish a clear record of what [the] applicant intends to claim." *Ibid.* If such a construction yields more than one plausible interpretation of a claim during examination, the PTO appropriately requires the applicant "to more precisely define the metes and bounds of the claimed invention." *Miyazaki*, 2008 WL 5105055, at *5-*6; see *PTO Definiteness Guidelines*, 76 Fed. Reg. at 7164; *Halliburton*, 514 F.3d at 1255.

In contrast, when a patent is under review before a court, the patent enjoys a statutory presumption of validity, see 35 U.S.C. 282, and the court generally has access to a fuller prosecution record from which the meaning of claim terms can be gleaned, *PTO Definiteness Guidelines*, 76 Fed. Reg. at 7164. At that juncture, courts appropriately require challengers to overcome the presumption of validity by offering a persuasive demonstration of indefiniteness, including a showing that reasonable efforts at claim construction are unavailing. See *Exxon*, 265 F.3d at 1375; see also *PTO Definiteness Guidelines*, 76 Fed. Reg. at 7164 ("[W]hen possible, courts construe patented claims in favor of finding a valid interpretation."). Petitioners are therefore wrong in asserting (Pet. 23) that the PTO "has expressly rejected the statutory test employed by the Federal Circuit." Both entities inquire whether a person skilled in the art would understand what is being claimed in light of the intrinsic evidence, and both acknowledge the different roles each entity serves in the patent process. See *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997); *PTO Definiteness Guidelines*, 76 Fed. Reg. at 7164.

C. The Court Of Appeals' Decision Is Correct

The court of appeals correctly held that the challenged claims, when construed in light of the specification and the relevant prosecution history, are sufficiently definite to allow a person skilled in the art of designing and labeling nucleic acid probes to understand the scope of respondents' invention. The patents disclose a technique for labeling nucleic acid probes without using costly, unstable, and potentially dangerous radioisotopes. Pet. App. 3a-6a. That technique employs "linkage groups" covalently bonded to the polynucleo-

tide probe to hold a signaling moiety (*e.g.*, a fluorescent dye) physically separated from the probe in a manner that "does not interfere substantially" with the ability of the probe to hybridize with the target nucleic acid, or with the ability of scientists to detect the signal after hybridization. *Ibid.*

Petitioners contend (Pet. 21-23, 26-29) that the claim terms are invalid because the phrase "not interfering substantially" does not provide the requisite notice of the "boundaries" of what is being claimed. In particular, petitioners argue both that the challenged claims are invalid because they merely provide "examples of what the patent is meant to cover" (Pet. 21), and because practitioners would need to engage in experimentation to determine whether a particular linkage group would be covered (Pet. 27-28). The court of appeals correctly rejected those arguments.

The Federal Circuit appropriately concluded that the claims at issue are definite because the intrinsic evidence "provides 'a general guideline and examples sufficient to enable a person of ordinary skill in the art to determine [the scope of the claims].'" Pet. App. 16a-17a (quoting *In re Marosi*, 710 F.2d 799, 803 (Fed. Cir. 1983)) (brackets in original). For example, the specification identifies the preferred type and structure of the linkage group, as well as the preferred method of binding the group to the probe. See *id.* at 15a-17a. The specification also identifies "essential criteria" for selecting a linkage group and teaches that the melting temperatures (as determined by the thermal denaturation profile) and hybridization properties of target polynucleotides "can be used to measure the degree to which a linkage group interferes with hybridization."

Id. at 15a (quoting '824 patent specification, col. 18, ll.61-62).

As a person skilled in the art would know, melting temperature can be used as a proxy for the strength of the hydrogen bonds that form between hybridized strands of complementary DNA: a lower melting point indicates fewer or weaker bonds. Pet. App. 17a. A decrease in the melting temperature of a hybridized probe, relative to that of an unmodified control molecule, therefore provides an objective gauge for measuring the degree of interference with hybridization attributable to the linkage group attached to the probe. *Id.* at 15a-16a. The specification gives several examples of acceptable decreases of melting temperatures for DNA probes having a specified length and sequence. See *id.* at 16a. The court of appeals therefore concluded that, "[w]hen deciding whether a particular linkage group is or is not 'substantially' interfering with hybridization * * * , a person of ordinary skill would likely look to the thermal denaturation profiles and hybridization properties * * * of the modified nucleotide, to see whether they fall within the range of exemplary values disclosed in the intrinsic evidence." *Id.* at 17a.

The court of appeals further found that a skilled practitioner would draw reasonable inferences from the specific examples provided in the claims, specification, and prosecution history of linkage groups that satisfy the requirements of the invention. Pet. App. 14a, 16a. Dependent claims in the '824 and '767 patents, for example, recite a linkage group with a specific chemical structure. *Id.* at 14a. A person skilled in the art therefore would "presume[] that the term 'not interfering substantially' in the independent claims allows for at least as much interference as that exhibited when the linkage

group has the structure specified in the dependent claims." *Ibid.* In overcoming an initial indefiniteness rejection by the PTO, respondents also provided a declaration listing eight specific examples of linkage groups that did not substantially interfere with hybridization or detection. *Id.* at 16a.

The court of appeals also correctly rejected petitioners' objection that the claims were indefinite because a particular linkage group would fall within the scope of the patent with respect to some polynucleotides but not with respect to others. Pet. App. 18a. The Federal Circuit's analysis is in keeping with *Eibel Process*, in which this Court upheld the use of a term of degree as a reasonable solution to the problem of describing a wide variety of alternative arrangements that a person skilled in the art would recognize as sufficient to serve the purposes of the invention. 261 U.S. at 65-66; see pp. 10-11, *supra*. Indeed, respondents overcame an indefiniteness rejection by the PTO by demonstrating to the satisfaction of the examiner that a skilled practitioner would recognize that a "wide structural variety" of linkage groups, consistent with the teachings of the specification, would enable the invention to work. Br. in Opp. App. 44a. As the PTO has stated, "[a] broad claim is not indefinite merely because it encompasses a wide scope of subject matter provided the scope is clearly defined." *PTO Definiteness Guidelines*, 76 Fed. Reg. at 7164.

Petitioners' overarching objection (Pet. 27) is that "the Federal Circuit has permitted data points to substitute for boundaries, contrary to the statutory requirement of particularity and distinctness." But the court of appeals correctly concluded that the specification and prosecution history provide enough detail for a person skilled in the art to understand the scope of the claims.

That is sufficient to satisfy Section 112's definiteness requirement. Cf. *Minerals Separation*, 242 U.S. at 270 ("[T]he certainty which the law requires in patents is not greater than is reasonable."). And in any event, the court of appeals appears to have construed the claims to encompass only modified polynucleotide probes having "thermal denaturation profiles and hybridization properties * * * [that] fall *within the range of exemplary values disclosed* in the intrinsic evidence." Pet. App. 17a (emphasis added). As this Court has explained, it is well within the authority of a court to construe patent claims narrowly to avoid any ambiguity and preserve the proper scope of the invention. *Smith* v. *Snow*, 294 U.S. 1, 14 (1935); *McClain*, 141 U.S. at 425. The construction adopted by the court of appeals will control on remand, both for purposes of infringement and for evaluating petitioners' arguments concerning anticipation.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

NEAL KUMAR KATYAL
Acting Solicitor General

TONY WEST
Assistant Attorney General

MALCOLM L. STEWART
Deputy Solicitor General

SARAH E. HARRINGTON
Assistant to the Solicitor General

SCOTT R. MCINTOSH
MARK R. FREEMAN
Attorneys

BERNARD J. KNIGHT, JR.
General Counsel

RAYMOND T. CHEN
Solicitor and Deputy General Counsel

NATHAN K. KELLEY
KRISTI L.R. SAWERT
AMY J. NELSON
Associate Solicitors
U.S. Patent and Trademark Office

MAY 2011

174 (3)

No. 10-426

Supreme Court, U.S.
FILED
OCT 28 2010
OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

APPLERA CORP., ET AL.,

Petitioners,

v.

ENZO BIOCHEM, INC., ET AL.

Respondents.

ON PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF AMICI CURIAE ALTERA CORPORATION; CISCO SYSTEMS, INC.; THE COMPUTER & COMMUNICATIONS INDUSTRY ASSOCIATION (CCIA); GENERAL MOTORS, LLC; GOOGLE INC.; GUIDEWIRE SOFTWARE; INTUIT INC.; MICROSOFT CORPORATION; SAP AMERICA, INC.; AND SHORETEL IN SUPPORT OF PETITIONERS

T. ANDREW CULBERT
ISABELLA FU
MICROSOFT CORPORATION
One Microsoft Way
Redmond, WA 98052

MARK LEMLEY
Counsel of Record
CLEMENT S. ROBERTS
DURIE TANGRI LLP
217 Leidesdorff St.
San Francisco, CA 94111
(415) 362-6666
mlemley@durietangri.com

Counsel For Amici Curiae

233055

COUNSEL PRESS
(800) 274-3321 • (800) 359-6859

TABLE OF CONTENTS

	Page
TABLE OF CONTENTS	i
TABLE OF CITED AUTHORITIES	ii
INTEREST OF *AMICI CURIAE*	1
I. INTRODUCTION	3
II. ARGUMENT	4
A. The Definiteness Requirement Exists to Put the Public on Notice of What a Patent Covers	4
B. The Federal Circuit's "Insolubly Ambiguous" Test Frustrates the Goal of Providing the Public with Notice of What is Claimed	6
C. The Federal Circuit's Test Is Inconsistent with the Patent and Trademark Office's Approach and the Approach of the Regional Circuits	12
D. Patentees Take Advantage of the Federal Circuit's Lower Standard to Bring Meritless Claims	15
E. The Proper Approach Would Give Reasonable Notice of Claims' Meaning	18
F. This Court Should Take This Case to Revitalize the Law of Indefiniteness	18
III. CONCLUSION	19

TABLE OF CITED AUTHORITIES

Page

CASES

All Dental Produx, LLC v. Advantage Dental Prod. Inc., 309 F.3d 774 (Fed. Cir. 2002) 5

Altoona Publix Theaters v. Am. Tri-Ergon Corp., 294 U.S. 477 (1935) 4

Antonious v. ProGroup, Inc., 699 F.2d 337 (6th Cir. 1983) 14

Atmel Corp. v. Info. Storage Devices, Inc., 198 F.3d 1374 (Fed. Cir. 1999) 10

Bancorp Servs., L.L.C. v. Hartford Life Ins. Co., 359 F.3d 1367 (Fed. Cir. 2004) 6

Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448 (Fed. Cir. 1998) 10

Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342 (Fed. Cir. 2005) 6, 8

Enzo Biochem, Inc. v. Applera Corp., 605 F.3d 1347 (Fed. Cir. 2010) 8, 13

Ex Parte Miyazaki, 89 U.S.P.Q.2d 1207 (BPAI 2008) 12

Cited Authorities

	Page
Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371 (Fed. Cir. 2001)	6
General Elec. Corp. v. Wabash Appliance Corp., 304 U.S. 364 (1938)	4
Haemonetics Corp. v. Baxter Healthcare Corp., 607 F.3d 776 (Fed. Cir. 2010)	9
Halliburton Energy Serv. Inc. v. M-I, LLC, 514 F.3d 1244 (Fed. Cir. 2008)	9
Hearing Components Inc. v. Shure Inc., 600 F.3d 1357 (Fed. Cir. 2010)	5, 10
Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996)	4
McClain v. Ortmayer, 141 U.S. 419 (1891)	4
Newell Companies, Inc. v. Kenny Manufacturing Co., 864 F.2d 757 (Fed. Cir. 1988)	10
Norton Co. v. Bendix Corp., 449 F.2d 553 (2d Cir. 1971)	13-14
Permutit Co. v. Graver Co., 284 U.S. 52 (1931)	4

Cited Authorities

Page

Personalized Media Commc'n, LLC v. Int'l Trade Comm'n,
161 F.3d 696 (Fed. Cir. 1998) 10

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005) 9

Praxair, Inc. v. ATMI, Inc.,
543 F.3d 1306 (Fed. Cir. 2008) 8, 10

SSIH Equip., S.A. v. Int'l Trade Comm'n,
718 F.2d 365 (Fed. Cir. 1983) 11

United Carbon v. Binney & Smith Co.,
317 U.S. 228 (1942) 5, 6, 11

STATUTES

35 U.S.C. §§ 101 1

35 U.S.C. § 112 ..... 3, 6

OTHER AUTHORITIES

John R. Allison *et al.*, *Patent Quality and Settlement Among Repeat Patent Litigants*,
99 GEO. L.J. __ (forthcoming 2011) 15, 16

AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION,
REPORT OF THE ECONOMIC SURVEY 22 (2009) 16

Cited Authorities

Page

JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE: HOW JUDGES, BUREAUCRATS AND LAWYERS PUT INNOVATORS AT RISK 127 (2008) 16

Christa J. Laser, *A Definite Claim on Claim Indefiniteness: An Empirical Study of Definiteness Cases of the Past Decade with a Focus on the Federal Circuit and the Insolubly Ambiguous Standard*, 11 CHI.-KENT J. INTELL. PROP. 25 (2010) 11

Stephen M. McJohn, *Patents: Hiding From History*, 24 SANTA CLARA COMP. & HIGH TECH. L.J. 961 (2008) 13

Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, 9 LEWIS & CLARK L. REV. 231 (2005) 8

CONSTITUTIONAL PROVISIONS

U.S. Const., art. I, § 8, cl. 8. 1

INTEREST OF *AMICI CURIAE*[1]

Amici are among the most innovative corporations in the world. *Amici* collectively hold tens of thousands of patents that have been prosecuted in compliance with the Patent Act, 35 U.S.C. §§ 101 et seq., and have been involved in patent litigation as both plaintiffs and defendants. *Amici* are also frequent targets of infringement lawsuits based on patents of questionable validity, including patents containing ambiguously drafted claims. *Amici* have a strong interest in ensuring that the patent law is interpreted to serve its constitutional purpose of promoting the progress of science and useful arts, U.S. Const., art. I, § 8, cl. 8, and in particular, that claims be sufficiently definite so as to provide meaningful notice to other market participants.

Altera Corporation is a developer of programmable logic solutions, providing FPGAs, CPLDs and ASICs, along with design resources including development software, intellectual property cores and development kits, to more than 12,000 customers worldwide.

Cisco Systems, Inc. is a leader in designing, manufacturing and selling Internet Protocol-based networking and other products related to the

---

1. No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than the amici curiae, or their counsel, made a monetary contribution intended to fund its preparation or submission. The parties have been given appropriate notice and have consented to the filing of this brief. Such consents are being lodged herewith.

communications and IT sectors and provides services associated with their product. Cisco has over 8,000 issued United States patents.

The Computer & Communications Industry Association (CCIA) is an international, non-profit trade association of Internet, information technology, and communications companies, whose members employ more than 600,000 workers and generate annual revenues in excess of $200 billion. A list of CCIA members is available online at www.ccianet.org/members.

General Motors, LLC is part of the General Motors Company, one of the world's largest and most innovative automakers, with operations employing 205,000 people in every major region of the world and doing business in some 157 countries.

Google Inc. is an innovative technology company dedicated to the mission of organizing the world's information and making it accessible to millions of users around the world each day. Google develops and serves a broad range of internet services, including search, advertising, collaboration and mobile services.

Guidewire Software is a leading provider of enterprise software to the Property and Casualty Insurance industry.

Intuit Inc. is a leading provider of financial management, tax and online banking solutions for consumers, small and mid-sized businesses, accountants, and financial institutions.

Microsoft Corporation is one of the largest software companies in the world, providing innovative productivity solutions and other services to businesses and individuals.

SAP America, Inc. is a leading technology company focused on developing innovative software and computer-based business solutions.

ShoreTel is a leading provider of internet protocol (IP) unified communications solutions for businesses.

I. INTRODUCTION

Patent claims exist both to define and to put the public on notice of the scope of the patentee's property rights. To do this effectively, claims must be *definite*: they must allow a person of ordinary skill in the art to read and understand both what is claimed and what is not claimed. 35 U.S.C. § 112 ¶2.

The Federal Circuit's test for indefiniteness conflicts with this purpose. Under Federal Circuit law, a claim will not be invalidated as indefinite unless it has *no* discernible meaning. Claims that have multiple meanings are considered definite even where a person of ordinary skill in the art would not be able reliably to discern the claim's scope from among the possible alternatives. Thus, even where a person of ordinary skill in the art reasonably could interpret a claim in several different ways, and even where this ambiguity prevents the public from having notice of the claims' scope, the Federal Circuit will find the claim definite.

This approach is both legally wrong and bad policy. It is legally wrong because it is inconsistent with the approach set forth in this Court's precedents and enacted by Congress in the Patent Act. It is bad policy because it undermines the notice function of patent claims, promotes ambiguous claim drafting, and encourages frivolous litigation. For these reasons, and as set forth below, the

Court should grant *certiorari* and realign the governing law with the statutory objectives of the Patent Act.

II. ARGUMENT

A. The Definiteness Requirement Exists to Put the Public on Notice of What a Patent Covers

The purpose of a patent claim is to define the scope of the patentee's property rights. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996) ("The claim 'define[s] the scope of a patent grant'"); *Altoona Publix Theaters v. Am. Tri-Ergon Corp.*, 294 U.S. 477 (1935) ("Under the statute, it is the claims of the patent which define the invention.").

The bounds of this definition need to be clear because the claim secures "all to which [the patentee] is entitled" while "apprising the public of what is still open to them." *McClain v. Ortmayer,* 141 U.S. 419, 424 (1891). As Justice Brandeis explained, "[t]he statute requires the patentee ... to inform the public during the life of the patent of the limits of the monopoly asserted, so that it may be known which features may be safely used or manufactured without a license and which may not." *Permutit Co. v. Graver Co.*, 284 U.S. 52, 60 (1931); *see also General Elec. Corp. v. Wabash Appliance Corp.*, 304 U.S. 364, 368-69 (1938) ("The limits of a patent must be known for the protection of the patentee, the encouragement of the inventive genius of others, and the assurance that the subject of the patent will be dedicated ultimately to the public.").

The Federal Circuit has acknowledged that "the purpose of the definiteness requirement is to ensure that 'the claims, as interpreted in view of the written description, adequately perform their function of notifying the public of the scope of the patentee's right to exclude.'" *Hearing Components, Inc v. Shure Inc.*, 600 F.3d 1357 (Fed. Cir. 2010); *see also All Dental Produx, LLC v. Advantage Dental Prod. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002) ("The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, *e.g.*, competitors of the patent owner, can determine whether or not they infringe.").

This public notice function is, however, frustrated where competitors cannot read claims and understand what they cover and what they do not. *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942) ("The statutory requirement of particularity and distinctness in claims is met only when the inventor clearly distinguishes what is claimed from what went before in the art and clearly circumscribes what is foreclosed from future enterprise."). A claim must not be so ambiguous that persons of ordinary skill in the art cannot reasonably be expected to understand its scope. Yet, as discussed further below, that is precisely the result of the Federal Circuit's test.

B. The Federal Circuit's "Insolubly Ambiguous" Test Frustrates the Goal of Providing the Public with Notice of What is Claimed

This Court has noted that, when it comes to patent law, a "zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field." *United Carbon v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942). By structuring the law of indefiniteness so that claims are found valid even where they are susceptible to a wide variety of reasonable interpretations, the Federal Circuit has created just such a zone.

In particular, the Federal Circuit refuses to find indefiniteness "if the meaning of the claim is discernible, even though ... the conclusion may be one over which reasonable persons will disagree." *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001). As a result, "[o]nly claims 'not amenable to construction' or 'insolubly ambiguous' are indefinite" and claims are held definite if the terms "can be given *any* reasonable meaning." *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005) (emphasis added); *see also Bancorp Servs., L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1371 (Fed. Cir. 2004) ("if the claim is subject to construction, *i.e.*, it is not insolubly ambiguous, it is not invalid for indefiniteness.").

This standard is in direct conflict with the statutory requirement that a patent must set forth "claims particularly pointing out and distinctly claiming the subject matter" of the invention. 35 U.S.C. 112 ¶2. Even

claims that are not "particular" and "distinct" may nevertheless be given *some* reasonable meaning. To put it differently, the Federal Circuit has, by adopting the "insolubly ambiguous" standard, substantially departed from the underlying statutory language in a way that (as discussed further below) frustrates the underlying public policy.

For example, under this standard claims (including the one at issue in the present case) are held valid even when they are susceptible to *multiple* constructions, such that people of ordinary skill in the art cannot reasonably be expected to know which of the possible constructions is proper. So long as *some* reasonable meaning can be assigned by the court at the end of the day, the claim is held not indefinite, even where many such meanings of radically different claim scope are equally plausible.

As Judge Plager explained in dissenting from the Federal Circuit's decision to deny the defendant's rehearing petition in this case:

> the corollary derived from [the insolubly indefiniteness standard] is that if several persons of ordinary skill come up with competing but plausible interpretations of a disputed term . . . the problem is not one of an inherently ambiguous and potentially indefinite claim term, but rather the problem becomes simply one of picking the 'right' interpretation for that term. Since picking the 'right' interpretation—claim construction—is a matter of law over which this court rules, and since the view of the trial judge hearing the case is given little

> weight, . . . it is not until three court of appeals judges randomly selected for that purpose pick the 'right' interpretation that the public, not to mention the patentee and its competitors, know what the patent actually claims.

Pet. App. 76a-77a.

The Federal Circuit has tried to surmount this problem by adopting an approach premised on the idea that it is possible to decide between different plausible constructions by applying the available doctrines of claim construction in a principled manner. *See Datamize LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1348 (Fed. Cir. 2005) ("In the face of an allegation of indefiniteness, general principles of claim construction apply."); *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008) ("Indefiniteness is a matter of claim construction, and the same principles that generally govern claim construction are applicable..."). But this premise is not correct or supported by the data.

Indeed, the data shows that the Federal Circuit reverses challenged claim constructions on appeal nearly 40% of the time. Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, 9 LEWIS & CLARK L. REV. 231, 239 (2005). If it were really possible to reliably decide between equally plausible constructions through application of claim construction principles, the district courts (whose expertise in claim construction far exceeds that of most hypothetical scientific experts) would not be getting it wrong nearly half the time. It makes no sense to assert that virtually all claims are sufficiently definite to put the public on notice

of what is claimed, while the district courts' chance of correctly divining the scope of a patent's claims is little better than a coin flip.

For several reasons, the principles of claim construction often fail to provide meaningful guidance about which of several possible scopes a patent claim actually covers. First, courts can look to a very wide array of sources—both intrinsic and extrinsic—from which to derive a construction. *See Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (sources that may be used in claim construction include claim language, the specification, prosecution history, general and technical dictionaries, treatises, expert testimony, and multiple canons of interpretation). And many of those interpretive sources, including dictionaries and expert testimony, are not readily available to those reading a patent to determine its scope. Indeed, in *Phillips*, the Federal Circuit acknowledged that "there is a virtually unbounded universe of potential extrinsic evidence ... that could be brought to bear on any claim construction question." *Id.* at 1318.

The problem is further compounded by the Federal Circuit's misapplication of the "clear and convincing evidence" standard to determinations of indefiniteness. *See, e.g., Halliburton Energy Serv. Inc. v. M-I, LLC*, 514 F.3d 1244, 1249-50 (Fed. Cir. 2008) (the insolubly ambiguous "standard is met where an accused infringer shows by clear and convincing evidence that a skilled artisan could not discern the boundaries of the claim based on the claim language, the specification, and the prosecution history, as well as her knowledge of the relevant art area."); *Haemonetics Corp. v. Baxter Healthcare Corp.*, 607 F.3d 776, 783 (Fed. Cir. 2010) (same);

Hearing Components Inc. v. Shure Inc., 600 F.3d 1357, 1366 (Fed. Cir. 2010) (same).

Leaving aside the question of whether or not questions of invalidity should generally be judged by the clear and convincing evidence standard,[2] the Federal Circuit's application of an evidentiary standard to questions of definiteness makes no sense. Indefiniteness is an issue of claim construction and therefore a pure issue of law. *See Personalized Media Commc'ns, LLC v. Int'l Trade Comm'n*, 161 F.3d 696, 705 (Fed. Cir. 1998) ("A determination of claim indefiniteness is a legal conclusion that is drawn from the court's performance of its duty as the construer of patent claims."); *Atmel Corp. v. Info. Storage Devices, Inc.*, 198 F.3d 1374, 1377 (Fed. Cir. 1999) ("Indefiniteness, therefore, like claim construction, is a question of law that we review de novo."); *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008) ("Indefiniteness is a matter of claim construction, and ... a question of law"); *cf. Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc) (holding that claim construction is a question of law reviewed *de novo*).

An *evidentiary* standard, on the other hand, applies only to questions of fact. As the Federal Circuit described the distinction in *Newell Companies, Inc. v. Kenny Manufacturing Co.*, 864 F.2d 757, 767 (Fed. Cir. 1988), "[q]uantums of proof relate to proof of facts, not legal conclusions." *See also SSIH Equip., S.A. v. Int'l Trade*

---

2. As explained by many of the amicus briefs filed in support of the Petition for Certiorari in *Microsoft Corporation v. i4i*, No. 10-290, there are substantial questions about whether the "clear and convincing" evidence standard is appropriate for questions of validity, and if it is appropriate, when. This brief does not address these questions.

Comm'n, 718 F.2d 365, 375 (Fed. Cir. 1983) ("we find it inappropriate to speak in terms of a particular standard of proof being necessary to reach a legal conclusion. Standard of proof relates to specific factual questions.").

The Federal Circuit has not only conflated legal and factual questions, but also has built in precisely the zone of uncertainty that this Court warned against in *United Carbon*. Indeed, it is precisely where persons of ordinary skill in the art could reasonably disagree about the scope of the claim (i.e. where there is a zone of uncertainty about what the claims cover) that there will be a "dispute of fact" about what the claims cover and thus where, under the Federal Circuit's approach, the claim must be held valid.

The practical result of the Federal Circuit's test and the mistaken application of an evidentiary standard is that claims are rarely held indefinite, even where there is no reasonable way for people reading the patent to know *which* construction is correct and hence to know what is and is not covered by the claims. Indeed, at least one recent study suggests that, over the ten years period between 1998 and 2008, during which time the Federal Circuit applied the "insolubly ambiguous" standard, the percent of district court cases finding challenged claims to be definite has increased by sixty percentage points (from approximately 24% to approximately 84%).[3] Thus, the available data strongly suggests that the Federal Circuit's approach to the question of indefiniteness is a substantial factor in the outcomes of a meaningful number of cases.

---

3. Christa J. Laser, *A Definite Claim on Claim Indefiniteness: An Empirical Study of Definiteness Cases of the Past Decade with a Focus on the Federal Circuit and the Insolubly Ambiguous Standard*, 11 CHI.-KENT J. INTELL. PROP. 25 (2010).

C. The Federal Circuit's Test Is Inconsistent with the Patent and Trademark Office's Approach and the Approach of the Regional Circuits

As discussed previously, the Federal Circuit's approach to indefiniteness is at odds with the statutory requirement that a claim be sufficiently "distinct" and "particular" so as to provide notice of what is claimed and what is not claimed. It is, therefore, not surprising that the Federal Circuit's approach is also incompatible with the approach taken by other circuit courts and by the United States Patent & Trademark Office (PTO).

In contrast to the Federal Circuit, for example, the PTO's Board of Patent Appeals and Interferences (BPAI) has held (in a rare precedential opinion) that "rather than requiring that the claims are insolubly ambiguous, we hold that if a claim is amenable to two or more plausible claim constructions, the USPTO is justified in requiring the applicant to more precisely define the metes and bounds of the claimed invention by holding the claims unpatentable under 35 U.S.C. § 112, second paragraph, as indefinite." *Ex Parte Miyazaki*, 89 U.S.P.Q.2d 1207 (BPAI 2008), at *5.

While the BPAI pointed to the applicant's ability to fix claims during prosecution to justify its use of a lower standard than the one employed by the Federal Circuit, it is not clear why that difference should matter in light of the purpose of the definiteness requirement. As noted previously, the primary purpose of the definiteness requirement is to avoid ambiguity by putting the public on notice of what is and is not claimed by the patent. Restricting post-issuance indefiniteness challenges to situations in which there is *no* reasonable construction

for a claim term does nothing to eliminate that ambiguity. And it puts the burden on the wrong party. Why should the public bear the cost of that uncertainty when the applicant is in the best position to avoid it through careful claim drafting in the first instance? Indeed, as Judge Plager noted in his dissent to the *en banc* petition below, the patent prosecution literature actively *encourages* applicants to draft their claims in a purposefully ambiguous manner in order to impose these costs on competitors. *Enzo Biochem, Inc. v. Applera Corp.*, 605 F.3d 1347, 1348 n.2 (Fed. Cir. 2010) (Plager, J., dissenting from denial of rehearing). *See also* Stephen M. McJohn, *Patents: Hiding From History*, 24 SANTA CLARA COMP. & HIGH TECH. L.J. 961, 971 (2008) ("experts in claim drafting offer the following advice to inventors and patent drafters: Do not define the terms used in your claims; do not identify the category of invention in the preamble to the claims; do not identify features of the invention as "important;" and do not even use the word "invention" in the written description. Such claim drafting has been described as a trend toward 'intentional obscurity.'"). There is little to discourage applicants from drafting ambiguous claims when there is no downside (because they know that the claims will be held valid so long as *some* meaning can be assigned), and where the ambiguity otherwise resounds to the patent holder's benefit (because it allows them to alter the scope of the claim as later circumstances warrant).

The Federal Circuit rule also has created a circuit split on the issue of the proper standard for indefiniteness. Before 1982, when regional circuits heard patent infringement suits, they applied a more stringent standard. For example, in *Norton Co. v. Bendix Corp.*, 449 F.2d 553 (2d Cir. 1971), the Second Circuit found invalid as

indefinite a patent on a vacuum pump in which the nozzle was claimed as being "*closely spaced*" in relation to the lip and in which the guard ring extended a "*substantial distance* beyond said lip into the jet of vapor, thereby to condense the undesirably over-divergent portion of the vapor jet as it emerges from under the nozzle." The Court found that the italicized terms were indefinite because they did not "clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." To support this proposition the court noted that "there were several commercial compositions falling within the peripheral area of uncertainty" and found that this fact demonstrated that the claims "fail to inform the public as to what may or may not be manufactured." *Id.* at 557.

Under the Federal Circuit's current standards, as reflected in the decision below, *Norton* was incorrectly decided. After all, in the case below, the Federal Circuit found that the closely analogous phrase "not interfering substantially" was definite because there was "some standard for measuring that degree" insofar as "the claims in this case provide at least some guidance as to how much interference will be tolerated." Pet. App. 14a. The same thing was true in *Norton*, however, where the claims provided that the substantiality of the distance should be judged in terms of the resultant condensation of the vapor jet. The two cases are squarely and irreconcilably at odds with one another. *See also Antonious v. ProGroup, Inc.*, 699 F.2d 337, 340 (6th Cir. 1983) (finding indefinite a claim calling for a flexible fastener located on "the back portion of the glove extending from one edge of the opening to the other" despite the fact that the claim provided guidance on the purpose of the fastener and fact that the claim was

not insolubly ambiguous.) The Federal Circuit's "insolubly ambiguous" test heightens the standard the other regional Circuits used to judge indefiniteness and results in claims being upheld even where the ambiguity of those claims creates a substantial "zone of uncertainty" about the allowed scope of economic activity.

D. Patentees Take Advantage of the Federal Circuit's Lower Standard to Bring Meritless Claims

The law currently encourages applicants to draft ambiguous claims. Because the boundaries of these claims are indeterminate, patentees can and do file suit against products that are not within the proper scope of their patents. It has become common in recent years for plaintiffs to sue dozens of companies with vastly divergent products based on ambiguous patent claims covering inventions the plaintiffs never turned into products. There are literally hundreds of such cases filed each year.[4] Indeed, it is not uncommon for companies (including some of the *amici*) to have to defend against more than *thirty* patent litigations at any given time.

One problem that arises is that it is not uncommon for plaintiffs in these cases to seek to collect settlements of a few hundred thousand to a few million dollars from each of the defendants. Even where their patents are weak, they

---

4. Recent empirical evidence suggests that 83.2% of the most-litigated patents – the ones that involve the most suits against the most defendants – are filed by such non-practicing entities targeting an entire industry. John R. Allison et al., *Patent Quality and Settlement Among Repeat Patent Litigants*, 99 GEO. L.J. __ (forthcoming 2011), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1677785.

frequently succeed in this enterprise because the scope of the asserted patent's claims is unclear and so the cases are not subject to early summary judgment motions. Instead, defendants must choose between spending a great deal of money to litigate the case through claim construction before they can bring dispositive motions[5] or settling with the defendants. Not surprisingly, most settle, even when the underlying cases are weak.[6] This creates a substantial cost for businesses which, like some of the undersigned *amici*, may have dozens of patent lawsuits pending against them at any one time.[7] And, while the litigation-cost hold up problem in patent cases is not solely attributable to the Federal Circuit's indefiniteness standard, the undersigned *amici* strongly believe it is a substantial contributing factor because it encourages ambiguous claim drafting.

Even where the plaintiffs are not simply using transaction costs to extract settlements, ambiguous patents can result in meritless litigation. Some plaintiffs, for example, assert ambiguous patents against large companies in the hopes of winning a sizable judgment.

---

5. A recent survey of intellectual property firms reports that the average cost in legal fees to take a large patent case to trial is $5.5 million per side. AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION, REPORT OF THE ECONOMIC SURVEY 22 (2009).

6. Allison et al., *supra*, find that 89.6% of all non-practicing entity suits settle, despite the fact that when such cases go to judgment, the non-practicing patentee wins only 8% of the time.

7. *See* JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE: HOW JUDGES, BUREAUCRATS AND LAWYERS PUT INNOVATORS AT RISK 127 (2008) ("We thus conclude that patent litigation is a real problem for innovators and it does impose a cost on investment in innovation.")

These enormous judgments, while uncommon, have an outsized impact. Where claims are ambiguous enough that no one can tell in advance what such a claim covers, the resulting uncertainty can be debilitating for companies that must decide whether to litigate or license the patent.

The proliferation of ambiguous patent claims also increases the time, cost and expense of reviewing patents and of working around them. This is highly undesirable from the perspective of public policy. Companies should be encouraged and rewarded for their efforts to read patents, both because that behavior increases the dissemination of the information contained in the patent specification and because, insofar as companies can understand and work around the inventions claimed in the patents they review, it reduces litigation.

Problems associated with ambiguous patent claims are compounded by the dramatic increase in the number of patents over time. From 1963 to 2009, for example, the number of utility patents granted per year expanded from fewer than 46,000 to more than 167,000 – a nearly fourfold increase.[8] And because the effect is cumulative, the number of *outstanding* patents has grown even more dramatically – indeed, approximately one and a half times as many patents have been issued *since* 1996 than were issued in *all years prior* to 1996.[9] Unless patents provide robust notice of what they cover and what they do not cover, the ever-increasing number of outstanding patents

---

8. http://www.uspto.gov/web/offices/ac/ido/oeip/taf/us_stat.htm.

9. http://www.uspto.gov/web/offices/ac/ido/oeip/taf/apat.htm#PartA1_1.

of ambiguous scope will impose larger and larger costs on innovative companies. This problem is especially severe in the fastest growing areas of the economy, where the high density of patents makes it critical to have well-defined claims with discernible boundaries.

E. The Proper Approach Would Give Reasonable Notice of Claims' Meaning

Amici respectfully suggest that the proper standard for judging definiteness should be drawn directly from the purpose of that requirement. In particular, a claim should be held invalid as indefinite if a person of ordinary skill in the art would not know, in advance and with reasonable particularity, what the claim covers and what it does not cover. To put it differently, if a reasonable person of ordinary skill in the art could not be expected to know the metes and bounds of the claim, the claim is not sufficiently definite to provide adequate public notice.

By adopting a standard based on the notice function of the definiteness requirement, the Court would breathe life into the idea that patent claims should provide reasonable notice of what they cover.

F. This Court Should Take This Case to Revitalize the Law of Indefiniteness

The Federal Circuit continues to use a standard for evaluating indefiniteness that conflicts with this Court's precedents, even where, as in this case, the issue was squarely presented in an *en banc* petition and where a respected senior Federal Circuit judge urged the court to reconsider. If this Court does not act, there will be little

or no incentive for future litigants to raise the issue in the lower courts. Moreover, this is not a case where the Federal Circuit's law differs from the law of this Court by a matter of degree or in ways that are unlikely to matter. Instead, as discussed above, the Federal Circuit's law in this area directly subverts the purpose of the definiteness requirement, contravenes the principles established by this Court, mistakes an issue of law for an issue of fact, and conflicts with the approaches taken by both the Patent and Trademark Office and the other regional Circuit courts.

III. CONCLUSION

The petition for certiorari should be granted.

Respectfully Submitted,

MARK LEMLEY
Counsel of Record
CLEMENT S. ROBERTS
DURIE TANGRI LLP
217 Leidesdorff St.
San Francisco, CA 94111
(415) 362-6666
mlemley@durietangri.com

Counsel For Amici Curiae

T. ANDREW CULBERT
ISABELLA FU
MICROSOFT CORPORATION
One Microsoft Way
Redmond, WA 98052

Supreme Court, U.S.
FILED
OCT 28 2010
OFFICE OF THE CLERK

No. 10-426

In the Supreme Court of the United States

APPLERA CORP. AND TROPIX, INC.,
Petitioners,

v.

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC., AND YALE UNIVERSITY,
Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR YAHOO!, INC. AS *AMICUS CURIAE* SUPPORTING PETITIONERS

JASON C. WHITE
HOWREY LLP
321 North Clark Street
Chicago, IL 60610
(312) 595-2250

William C. Rooklidge
Counsel of Record
HOWREY LLP
4 Park Plaza, Suite 1700
Irvine, CA 92614
(949) 721-6900
RooklidgeW@howrey.com

Kevin T. Kramer
Yahoo!, Inc.
701 First Avenue
Sunnyvale, CA 94089
(408) 349-3300

Henry A. Petri, Jr.
HOWREY LLP
1111 Louisiana, 25th Floor
Houston, TX 77002
(713) 787-1400

Counsel for Amicus Curiae Yahoo!, Inc.

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D.C. 20002

TABLE OF CONTENTS

STATEMENT OF INTEREST OF *AMICUS CURIAE* 1

SUMMARY OF THE ARGUMENT 3

ARGUMENT 4

I. This Court Should Grant The Petition To Review Whether The Federal Circuit's Test For Claim Definiteness Conflicts With The Patent Statute And This Court's Precedent 4

A. The Patent Statute Requires More Than Patent Claims That Are "Capable Of Construction" 5

B. This Court's Decisions Emphasize The "Public Notice" Aspect Of Patent Claims 6

C. Under This Court's Precedent, If A Claim Read In View Of The Specification Description Fails To Clearly Establish What The Patentee Regards As His Invention, The Claim Is Invalid 10

II. This Court Should Grant Applera's Petition To Resolve The Uncertainty Created By The Federal Circuit's Indefiniteness Test 12

III. The Proper Approach Balances The Claim Construction Exercise And The Definiteness Requirement Of The Patent Statute 17

CONCLUSION 18

TABLE OF AUTHORITIES

Page(s)

Cases

Bedrock Computer Technologies LLC v. Softlayer Technologies, Inc., et al., No. 6:09-CV-269-LED-JDL (E.D. Tex.) 2

Bell Atlantic Network Srvs., Inc. v. Covad Communications Group, Inc., 262 F.3d 1258 (Fed. Cir. 2001) 17

Bright Response, LLC v. Google Inc., et al., No. 2:07-CV-371-CE (E.D. Tex.) 2, 14, 15, 16

General Electric Co. v. Wabash Appliance Corp., 304 U.S. 364 (1938) 11, 16, 18, 19

Honeywell Int'l, Inc. v. United States, 609 F.3d 1292 (Fed. Cir. 2010) 4

Innovad Inc. v. Microsoft Corp., 260 F.3d 1326 (Fed. Cir. 2001) 17

Merrill v. Yeomans, 94 U.S. 568 (1877) 10, 11, 12

Paid Search Engine Tools, LLC v. Yahoo! Inc., No. 2:07-CV-403-DF-CE (E.D. Tex.) 2

Permutit Co. v. Graver Corp., 284 U.S. 52 (1931) 3, 6, 12, 13

Power-One, Inc. v. Artesyn Techs., Inc., 599 F.3d 1343 (Fed. Cir. 2010) 4

The Incandescent Lamp Patent,
159 U.S. 465 (1895) 12

Ultimax Cement Mfg. Corp. v. CTS Cement Mfg. Corp.,
587 F.3d 1339 (Fed. Cir. 2009) 4

United Carbon Co. v. Binney & Smith Co.,
317 U.S. 228 (1942) ..... passim

Universal Oil Prods. Co. v. Globe Oil & Refining Co.,
322 U.S. 471 (1944) 7, 16

White v. Dunbar,
119 U.S. 47 (1886) 18

Statutes

35 U.S.C. § 111(a)(2)A) 11

35 U.S.C. § 112, ¶2 ..... 2, 5, 11

35 U.S.C. § 251 11

Rules

37 C.F.R. § 1.111(b) 11

37 C.F.R. § 1.111(c) 11

37 C.F.R. § 1.51(b)(1) 11

STATEMENT OF INTEREST OF *AMICUS CURIAE*

Yahoo!, Inc. ("Yahoo!") respectfully submits this brief in support of the petition of Applera Corp. and Tropix, Inc. (collectively "Applera").[1] Yahoo! is a high-technology leader, owning and operating one of the most frequently visited websites on the Internet. Yahoo! attracts hundreds of millions of users every month through its innovative technology and engaging content and services, including Internet search capabilities, e-mail, and instant messaging. Yahoo! invests millions of dollars on its research and development efforts, which have led to hundreds of patents protecting the technology at the heart of Yahoo!'s business. Accordingly, Yahoo! recognizes first-hand the importance of patents and a healthy patent system.

At the same time, Yahoo!'s various products and services are increasingly the targets of infringement assertions by others. For example, at the beginning of 2007, Yahoo! was a defendant in four patent infringement suits. In contrast, Yahoo! is currently defending over 20 patent infringement suits. Most of the increase is due to suits brought by

---

[1] Yahoo! provided counsel of record with notice of its intent to file this brief more than ten days prior to the due date, as required by Supreme Court Rule 37.2(a), and both Petitioners and Respondents have consented to the filing of *amicus curiae* briefs. Such consents are on file with the Court. In accordance with Supreme Court Rule 37.6, Yahoo! states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than Yahoo! or its counsel.

so-called non-practicing entities ("NPEs")—companies that do not practice their patented inventions, and many of which assert the patents in hopes of using the expense and uncertainties of litigation (particularly in jury cases) to obtain a windfall.

In several of its current cases, Yahoo! has argued that the asserted patent claims are invalid on the ground of indefiniteness. That is, Yahoo! has argued that the asserted claims fail to particularly point out and distinctly claim the subject matter that the patent applicant regards as his or her invention as required by 35 U.S.C. § 112, ¶2. *See Bright Response, LLC v. Google Inc., et al.*, No. 2:07-CV-371-CE (E.D. Tex.); *Paid Search Engine Tools, LLC v. Yahoo! Inc.*, No. 2:07-CV-403-DF-CE (E.D. Tex.); *Bedrock Computer Technologies LLC v. Softlayer Technologies, Inc., et al.*, No. 6:09-CV-269-LED-JDL (E.D. Tex.).

Based on Yahoo!'s balance of interests—as both owner of valuable patent rights and as the frequent target of infringement suits—Yahoo! respectfully provides its views on the critically important issue before this Court, *i.e.*, the proper standard for determining whether a patent claim is indefinite. Yahoo! hopes that the views expressed in this brief will assist the Court in deciding whether to address and resolve the important question presented by the petition.

SUMMARY OF THE ARGUMENT

This Court has long recognized that the statutory requirement that patents "particularly point[ ] out and distinctly claim[ ]" what the patentee regards as his invention exists for the benefit of the public. Without that "definiteness" requirement, there would be a "zone of uncertainty" around patent claims that competitors could enter only at the risk of an infringement suit. *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942). Patentees have the burden to draft clear patent claims to put the public on notice of "the limits of the monopoly asserted" so the public can know what features can be "safely used or manufactured without a license and which may not." *Permutit Co. v. Graver Corp.*, 284 U.S. 52, 60 (1931).

The Federal Circuit has adopted an indefiniteness standard that abandons the public notice function of patent claims. Under the Federal Circuit's test, a claim is indefinite only if it "cannot be construed" or is "insolubly ambiguous." That standard disregards the statute and this Court's precedent. Competitors and members of the public desiring to know what they can practice without fear of infringement liability no longer can rely on the words of patent claims. Instead, they have to incur the costs of litigation to determine whether a trial court (or the Federal Circuit) will find some "soluble" meaning to the patent claims or give them some claim construction. The Federal Circuit's standard thus exacerbates the "zone of uncertainty" surrounding ambiguous patent claims.

The proper approach ought to give effect to the statutory language and this Court's precedent. A patent claim is definite only if it "particularly point[s] out and distinctly claim[s]" the invention so as to give the public notice of what is infringing. An ambiguous claim cannot be saved through claim construction or by adding limitations from the preferred embodiment during the claim construction exercise. Otherwise, the "zone of uncertainty" remains and claims lose their public notice function.

This Court now has the ideal opportunity to resolve the uncertainty concerning patent claims that the Federal Circuit's indefiniteness test has created. The Court should therefore grant the petition for writ of certiorari.

ARGUMENT

I. THIS COURT SHOULD GRANT THE PETITION TO REVIEW WHETHER THE FEDERAL CIRCUIT'S TEST FOR CLAIM DEFINITENESS CONFLICTS WITH THE PATENT STATUTE AND THIS COURT'S PRECEDENT

As illustrated by its decision here, the Federal Circuit holds that a patent claim is indefinite only if it "cannot be construed" (Pet. App. 10a) or is "insolubly ambiguous." *See, e.g., Honeywell Int'l, Inc. v. United States*, 609 F.3d 1292, 1301-02 (Fed. Cir. 2010); *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1348 (Fed. Cir. 2010); *Ultimax Cement Mfg. Corp. v. CTS Cement Mfg. Corp.*, 587 F.3d 1339, 1352 (Fed. Cir. 2009). That standard, however, has no basis in the statute, and it is inconsistent with

this Court's precedent concerning the statutory definiteness requirement.

A. The Patent Statute Requires More Than Patent Claims That Are "Capable Of Construction"

The relevant section of the patent statute provides:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. § 112 ¶ 2. On its face, Section 112 ¶ 2 requires patent claims to "particularly point[ ] out and distinctly claim[ ]" what the patentee regards as his invention. The statute thus calls for more than claims that can somehow "be construed."

This Court's decision in *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228 (1942), illustrates that point. The two claims at issue recited "Su[b]stantially pure carbon black in the form of commercially uniform, comparatively small, rounded, smooth aggregates having a spongy or porous interior" and "As an article of manufacture, a pellet of approximately one-sixteenth of an inch in diameter and formed of a porous mass of substantially pure carbon black." *Id.* at 231-32. Based on the testimony of one of the inventors, the court was able to ascertain the meaning of each of the claim terms as used in the context of the patent:

"substantially pure," "commercially uniform," "comparatively small," "spongy," "porous," "pellet," and "approximately one-sixteenth of an inch in diameter." *Id.* at 233-34.

Despite those constructions, the Court held the claims indefinite because they failed both to distinguish the alleged invention from the prior art and to "clearly circumscribe what is foreclosed from future enterprise." *See id.* at 236-37. Under *United Carbon*, therefore, "definiteness" under the patent statute requires more than claims that are "amenable to construction."

B. This Court's Decisions Emphasize The "Public Notice" Aspect Of Patent Claims

This Court's precedent repeatedly emphasizes that patent claims have an important public notice function. As explained in *Permutit Co. v. Graver Corp.*, 284 U.S. 52, 60 (1931),

> The statute requires the patentee not only to explain the principle of his apparatus and to describe it in such terms that any person skilled in the art to which it appertains may construct and use it after the expiration of the patent, but also to inform the public during the life of the patent of the limits of the monopoly asserted, so that it may be known which features may be safely used or manufactured without a license and which may not.

See also, e.g., Universal Oil Prods. Co. v. Globe Oil & Refining Co., 322 U.S. 471, 484-85 (1944) ("The claim is the measure of the grant. The claim is required to be specific for the very purpose of protecting the public against extension of the scope of the patent.") (citation omitted); *United Carbon*, 317 U.S. at 233 ("To sustain claims so indefinite as to not to give the notice required by the statute would be in direct contravention of the public interest which Congress therein recognized and sought to protect.").

Thus, by requiring claims to "particularly point[ ] out and distinctly claim[ ]" the alleged invention, the definiteness requirement ensures there is no "zone of uncertainty" which "enterprise and experimentation may enter only at the risk of infringement claims." *United Carbon*, 317 U.S. at 326.

The indefiniteness test adopted by the Federal Circuit abandons that public notice function. Simply because a claim might be "amenable to construction" during litigation does not mean that the claim *per se* meets the statutory definiteness requirement. As explained above, this Court in *United Carbon* was able to determine the meaning of the patent claim terms, but nonetheless held the claims indefinite for failing to "clearly circumscribe what is foreclosed from future enterprise." *See United Carbon*, 317 U.S. at 236.

Applera's petition aptly illustrates the concern regarding the public notice function of patent claims. The '824 patent in suit included as one claim element "said linkage group not interfering substantially

with the characteristic ability of said compound to hybridize with said nucleic acid or of A to be detected." Pet. App. 5a (emphasis omitted). The Federal Circuit adopted the district court's construction of that element to mean "the linkage group neither substantially interferes with the ability of the compound to hybridize with the nucleic acid nor substantially interferes with the ability of A to be detected." *See* Pet. App. 7a, 12a-13a.

The court's claim construction merely reverses the word order of the phrase "interfering substantially," without giving any definition of how "substantial" any "interference" could be and still fall within the scope of the claims. Instead, the court cited examples from the specification from which one could supposedly determine how much was "substantial interference," including the description that "[i]t is even more preferred that the chemical linkage group be derived from a primary amine, and have the structure $-CH_2-NH-$ ...." Pet. App. 15a. Thus, according to the Federal Circuit, one skilled in the art could look to the specification examples to determine linkage groups that did not "substantially interfere."

The problem, however, is that some of the specification's examples are also in the prior art. *See* Pet. App. 20a ("[T]wo of Applera's prior art references ... employ a $-CH_2-NH-$ linkage group, which arguably belongs to the set of linkage groups disclosed in the patents-in-suit as 'even more preferred' embodiments."). Nevertheless, the Federal Circuit affirmed the denial of summary judgment of invalidity because, despite the

description of –CH_2–NH– linkage groups in the specification, Enzo's expert declared that the –CH_2–NH– linkage group of the prior art references would cause "substantial interference." *See* Pet. App. 21a-22a, 25a. The court noted that "there are an infinite variety of linkage groups 'derived from a primary amine, [with] the structure –CH_2–NH–' ... which suggests that not every 'even more preferred' linkage group would satisfy the not substantially interfering element." Pet. App. 24a.

According to the Federal Circuit's decision, the claims are definite because some examples cited in the specification *meet* the "substantially interfere" claim construction, while at the same time, the claims may not be anticipated because other examples cited as preferred embodiments in the specification *may not meet* the "substantially interfere" construction. Such a result fails to fulfill the public notice function of the claims. Because the patent provides no definition or meaningful explanation of "substantial interference," a competitor or other member of the public reading the Enzo patent specification could not know what linkage groups are within the scope of the claim. Under the Federal Circuit's decision, some example –CH_2–NH– linkage groups do not "substantially interfere" and are within the scope of the claims, while other example –CH_2–NH– linkage groups (per Enzo, the ones in the prior art) do "substantially interfere" and may be outside the claim scope—but the patent never explains the difference.

That result disregards the patent statute because, as this Court has stated, "[t]he statutory

requirement of particularity and distinctness in claims is met only when they clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." *United Carbon*, 317 U.S. at 236. Examples in a patent specification that may or may not be prior art and may or may not be within the scope of the claim—without any explanation of how to determine that—cannot meet the definiteness requirement of the statute.

C. Under This Court's Precedent, If A Claim Read In View Of The Specification Description Fails To Clearly Establish What The Patentee Regards As His Invention, The Claim Is Invalid

Given this Court's precedent, the patent statute requires claims to be more than simply "amenable to construction." Under that precedent, if a claim, read in view of the remainder of the specification, fails to clearly establish what the patentee regards as his invention, the claim falls short of the requirements for a monopoly grant and is invalid. *See Merrill v. Yeomans*, 94 U.S. 568, 573 (1877) ("The developed and improved condition of the patent law, and of the principles which govern the exclusive rights conferred by it, leave no excuse for ambiguous language or vague descriptions. The public should not be deprived of rights supposed to belong to it, without being clearly told what it is that limits these rights.")

Because the applicant is the author of the patent claims, the burden is on the patentee to

ensure that its claims "particularly point[ ] out and distinctly claim[ ]" the invention. *General Electric Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 372 (1938) ("Congress requires, for the protection of the public, that the inventor set out a definite limitation of his patent; that condition must be satisfied before the monopoly is granted."); *Merrill*, 94 U.S. at 573-74 ("It seems to us that nothing can be more just and fair both to the patentee and the public, than that the former should understand and correctly describe just what he has invented, and for what he claims a patent."). The inventor presumably understands what his invention is. The patent applicant is the author of the patent claims. 35 U.S.C. § 111(a)(2)A); 35 U.S.C. § 112 ¶ 2; 37 C.F.R. § 1.51(b)(1). And, during examination of the patent application, the applicant has the ability to present new claims and amend existing claims. 37 C.F.R. § 1.111(b), (c). Thus, at all stages of the application process, the patentee has the ability to draft claims that will particularly point out and distinctly claim his invention. Even after the patent issues, if it becomes apparent that the claims are indefinite, the patentee still has the remedy of reissue in order to clarify the claims. 35 U.S.C. § 251; *see Merrill*, 94 U.S. at 573 ("If the patentee is also entitled to a patent for the product of this distillation, and has failed, as we think he has, to obtain it, the law affords him a remedy, by a surrender and re-issue. When this is done, the world will have fair notice of what he claims of, what his patent covers, and must govern themselves accordingly.").

Furthermore, as explained above, this Court's precedent recognizes that the "particularity" and

"distinctness" requirement of the patent statute is in part for the benefit of competitors and the public. Not only does the patent inform courts "of what they are called upon to construe," it serves the separate function of "appris[ing] ... competing manufacturers and dealers of exactly what they are bound to avoid." *The Incandescent Lamp Patent*, 159 U.S. 465, 474 (1895). *See also Permutit*, 284 U.S. at 60 ("The statute requires the patentee ... *to inform the public during the life of the patent of the limits of the monopoly asserted*, so that it may be known which features may be safely used or manufactured without a license and which may not.") (emphasis added); *Merrill*, 94 U.S. at 573 ("*The public* should not be deprived of rights supposed to belong to it, without being clearly told what it is that limits these rights.") (emphasis added). Therefore, whether the claims can be construed in a legal proceeding using the legal fiction of the hypothetical person of ordinary skill in the art is not determinative of whether the claims satisfy the public notice function of the "definiteness" requirement.

II. THIS COURT SHOULD GRANT APPLERA'S PETITION TO RESOLVE THE UNCERTAINTY CREATED BY THE FEDERAL CIRCUIT'S INDEFINITENESS TEST

This Court's precedent recognizes that the statutory requirement that patent claims particularly point out and distinctly claim an invention exists so that competitors may know what is covered, and what is not, so there is no "zone of uncertainty" concerning the patent claims. *United Carbon*, 317 U.S. at 236 ("A zone of uncertainty

which enterprise and experimentation may enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field.").

By adopting a standard that holds claims indefinite only if they are "insolubly ambiguous" and not "amenable to construction," the Federal Circuit has in fact increased the "zone of uncertainty" surrounding patent claims. Under the Federal Circuit's test, competitors and other members of the public threatened with a patent having claims that are facially ambiguous cannot know whether they may be infringing until at least the conclusion of the claim construction proceedings. The public no longer can read the claims within the context of the patent to determine "which features may be safely used or manufactured without a license and which may not." *Permutit*, 284 U.S. at 60. Instead, competitors and other members of the public must face potential infringement suits and incur the costs of litigation at least through a formal claim construction to learn what the claims should have shown in the first place.

Yahoo! has experienced the "zone of uncertainty" the Federal Circuit's test has created in recent cases involving indefinite claims. As noted above, Yahoo! is facing an increasing number of infringement suits often brought by NPEs seeking to "monetize" patents they have purchased, either through a windfall jury verdict or a settlement. Several of those patents on their face seem to have no applicability to the products and services against which they are asserted, yet plaintiffs attempt to interpret the claims to cover Yahoo!'s business. In

those cases, Yahoo! has raised the defense of indefiniteness.

Because the Federal Circuit's test ties the statutory definiteness standard to the court's claim construction, parties seeking to stretch claims beyond the intended bounds of the patent are able to avoid the indefiniteness defense and increase Yahoo!'s costs to defend the suit. And if the court construes the claim, under the Federal Circuit's "not amenable to construction" standard, the claim will almost always be held definite, regardless of whether the claim as construed gives notice as to what infringes.

One recent example illustrates the point. In *Bright Response, LLC v. Google Inc.*, No. 2:07-CV-371-CE (E.D. Tex.), Bright Response, an NPE, sued Yahoo! for infringement of a patent with claims directed to a method of automatically interpreting and responding to electronic messages and that disclosed email messages as the preferred embodiment. Bright Response sought to read its patent claims on Yahoo!'s search advertising service. One independent method claim of Bright Response's patent included vague claim terms that were not defined in the specification and recited steps (a), (b), and (c). A dependent claim recited steps (b)(1)(i) and (ii) and (c) that, when added to the original method steps, formed a method that was not described in or supported by the specification. During claim construction, Yahoo! argued that the claim was indefinite based on the vague claim terms. In short, based on the claim language, it was impossible to determine whether step (b)(1) should be an

additional step or substituted for step (b) in the independent claim. The court ruled, however, that the claim was not "insolubly ambiguous" and rejected Yahoo!'s first indefiniteness argument. *See* Memorandum Opinion and Order at 8, No. 2:07-CV-371-CD, Dkt # 369 (E.D. Tex. June 18, 2010). The court also interpreted the method claim by ruling that "claim 28 requires the following steps: claim 26's step (a), claim 26's step (b), claim 28's step (b1), and claim 28's step (c)" rejecting Yahoo!'s second indefiniteness argument. *See* Memorandum Opinion and Order at 17, No. 2:07-CV-371-CD, Dkt # 369 (E.D. Tex. June 18, 2010). Because Yahoo!'s accused product performed its steps in a different order than required by the wording of the asserted claim, as construed by the court, Yahoo! prepared its noninfringement defense based on that claim construction.

In response to that noninfringement position, Bright Response's technical expert sought to testify that steps (b)(1) and (c) need not be performed in order. The district court granted Yahoo!'s request to exclude testimony inconsistent with the court's claim construction, namely that "step (b1) must occur before step (c)." Order, No. 2:07-CV-371-CD, Dkt # 594 (E.D. Tex. Aug. 3, 2010).

Yahoo! then continued its noninfringement defense based on that claim construction and its position that in its accused product step (b1) did not occur before step (c). On the third day of trial and at Bright Response's request, the court modified its claim construction, holding that step (c) was only "conditional" and "there is no order requirement

imposed on step (b1)(ii)." Order, No. 2:07-CV-371-CD, Dkt # 605 (E.D. Tex. Aug. 3, 2010).

Despite what Yahoo! thought was apparent from the face of the patent, the district court modified its claim construction mid-trial in response to Bright Response's arguments on claim construction made necessary by the specter of indefiniteness. That result is in direct contravention of the statutory requirement that the claims ought to have "particularly point[ed] out and distinctly claim[ed]" the invention "to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their rights." *General Electric*, 304 U.S. at 369. Bright Response obtained those "unreasonable advantages" first by alleging that claims directed to automatically responding to electronic messages covered Yahoo!'s advertising services, then by asking the court to re-construe the claims and expand their scope so as to rebut Yahoo!'s noninfringement positions based on the earlier claim constructions. *See Universal Oil Prods.*, 322 U.S. at 484-85 ("The claim is the measure of the grant. The claim is required to be specific for the very purpose of protecting the public against extension of the scope of the patent.") (citation omitted).

Under the Federal Circuit's "amenable to construction" test, however, the claims were not ruled indefinite, despite that Yahoo! had no notice of how it could be infringing until after three separate claim constructions by the district court.

III. THE PROPER APPROACH BALANCES THE CLAIM CONSTRUCTION EXERCISE AND THE DEFINITENESS REQUIREMENT OF THE PATENT STATUTE

United Carbon shows that claims may be indefinite even if the claims terms can be construed. Thus, the "zone of uncertainty" surrounding vague patent claims is avoided—not through claim construction or by a court determining whether the claims are "soluble"—but by the patentee drafting clear claims in the first place, putting the public and competitors on notice of what is foreclosed. The claim construction exercise should not be used to cure indefinite claims. Instead, the obligation to particularly point out and distinctly claim an invention is a separate requirement of the patent statute.

Also, it is well-established that, for purposes of claim construction, limitations from the description of the preferred embodiment cannot be read into claims. *Bell Atlantic Network Srvs., Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1270 (Fed. Cir. 2001) ("We are mindful of the fact that limitations from the specification may not be read into the claims."); *Innovad Inc. v. Microsoft Corp.*, 260 F.3d 1326, 1332 (Fed. Cir. 2001) (The "interpretative process forbids importing limitations from the specification into the defining language of the claims."). That same rule should apply for purposes of resolving an indefiniteness issue. If a claim is ambiguous on its face and could only be rendered definite by adding limitations from the preferred embodiment, then it is invalid. *General*

Electric, 304 U.S. at 374 (process limitations may not be read into the product claim to avoid indefiniteness: "to save the product claim in this fashion would constitute an improper importation into the claim of a factor nowhere described there.").

Permitting patent owners to treat a patent claim as a "nose of wax," re-wording its elements and adding limitations from the specification description in the guise of "construction," abandons the "public notice" function of claims. *Cf. White v. Dunbar*, 119 U.S. 47, 51 (1886) ("Some persons seem to suppose that a claim in a patent is like a nose of wax, which may be turned and twisted in any direction, merely by referring to the specification, so as to make it include something more than, or something different from, what its words express.") It is only by following the language of the statute and requiring patentees to "particularly point[ ] out and distinctly claim[ ]" the invention that the goal of public notice will be fulfilled and balance be restored to the patent system.

CONCLUSION

The patent statute and this Court's precedent require patentees to give notice to the public of what infringes by "particularly pointing out and distinctly claiming" the subject matter the patentee considers the invention. The Federal Circuit's rule that a claim is indefinite only if it is insolubly ambiguous and not amenable to construction eviscerates that requirement. Under the Federal Circuit's test, patent owners asserting patent against Yahoo! and others are effectively able to re-write their patent

claims until they obtain a claim scope to cover the accused products, without fear that the ever-changing claim scope could render the claim indefinite. As this Court has recognized, the patent statute places the burden on the patent applicant to write clear claims that particularly point out and distinctly claim the invention. Under the indefiniteness standard the Federal Circuit has adopted, however, the public has insufficient notice of what the claims cover, patentees can obtain "unreasonable advantages" (*General Electric*, 304 U.S. at 369), and there is a "zone of uncertainty" surrounding every patent that is not clear on its face. *United Carbon*, 317 U.S. 228.

The Court should grant Applera's petition and resolve the uncertainty that the Federal Circuit's indefiniteness standard has created.

Respectfully submitted.

JASON C. WHITE
HOWREY LLP
321 North Clark Street
Chicago, IL 60610
(312) 595-2250

Kevin T. Kramer
Yahoo!, Inc.
701 First Avenue
Sunnyvale, CA 94089
(408) 349-3300

William C. Rooklidge
Counsel of Record
HOWREY LLP
4 Park Plaza, Suite 1700
Irvine, CA 92614
(949) 721-6900

Henry A. Petri, Jr.
HOWREY LLP
1111 Louisiana, 25th Floor
Houston, TX 77002
(713) 787-1400

OCTOBER 28, 2010